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NEW ANESTHETIC DRUGS

Robert J. Fragen, MD, *Guest Editor*

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Guest Editor

Preface

The discovery that nitrous oxide and di-ethyl ether produce anesthesia occurred in the mid 1800s. Since then, a treatise could be written on what's new in the pharmacology of drugs used in the perioperative period. Until the past few decades, this subject could be covered in a single paper or a short report. The number of new drugs available to anesthesiologists is now at the point where we can devote an entire issue of *Anesthesiology Clinics of North America* to the subject.

The proliferation of new drugs and new facts about old drugs results from the endeavors of scientists in pharmaceutical companies, basic scientists in medicine, and clinical investigators. The observations of clinicians who use these drugs in their practice is also very important. Particularly encouraging, I believe, is the increasingly cooperative efforts between the pharmaceutical industry and the medical profession to develop new drugs to fill the perceived gaps in our ability to treat patients or to improve on the safety of drugs in current use.

I am pleased that physicians and basic scientists with research and teaching expertise in the subjects presented here, agreed to contribute to this issue. In each area, they attempt to bring you up to date on what's new. Each article contains many references from 1986 and 1987. Drs. Avram and Henthorn discuss the factors influencing drug kinetics and dynamics, so we can rationally plan drug infusions for intravenous agents.

Articles 2 through 6 cover the drugs used to produce the anesthetic state. Drs. Stoelting and Rosenfeld discuss the new volatile anesthetic, sevoflurane, the controversies of hepatotoxicity after enflurane and isoflurane, and the role of isoflurane in producing "coronary steal" in patients with coronary artery disease. Dr. White presents the latest on midazolam, etomidate, and propofol; agents that can be used to induce general anesthesia and maintain the hypnotic state under various conditions. He also describes the pharmacology of flumazenil, a specific benzodiazepine antagonist. Dr. Rosow presents data on the fentanyl derivatives, alfentanil and sufentanil. He also gives us a new look at the agonist-antagonist analgesics (kappa agonists) and presents data on a new, longer-acting opioid antagonist, nalmefene. Dr. Shanks discusses three new muscle relaxants that are currently undergoing clinical trials and what we have learned about atracurium and vecuronium since their release for general use in 1985. He presents a unique way to look at the concept of "cumulation" and an interesting description of the administration of nondepolarizing relaxants by continuous infusion. Although there are no recently released local anesthetics, rapivicaine and EMLA are undergoing clinical investigation, and other compounds are identified that have the potential of producing local anesthesia. These, in addition to the controversy of whether adjusting the pH of local anesthetics is valuable, are discussed by Drs. Arthur and Covino.

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I thank each of these authors for their contributions not only to this issue, but for adding to our medical knowledge through their research efforts. I also thank W.B. Saunders Company for choosing this subject for *Anesthesiology Clinics of North America* and for inviting me to be their guest editor.

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What's New in Pharmacokinetics and Pharmacodynamics?

Michael J. Avram, PhD, and Thomas K. Henthorn, MD†*

More than any other medical specialty, anesthesiology is intertwined with concepts of pharmacokinetics and pharmacodynamics. All practiced providers of anesthesia have strong intuitive senses of the phenomena others have described by extensive mathematical treatments.

Pharmacokinetic innovations often describe pharmacologic events seen with anesthetic drugs. It was Kety's 1951 description of the tissue distribution and pulmonary exchange of inert (anesthetic) gases that pioneered the field of physiologic pharmacokinetic modelling.[45] This was extended to intravenous anesthetics in 1960 by Price et al[61] when they provided the pharmacokinetic rationale for the 1952 observations of Brodie et al[11] that the rapid offset of the effect of thiopental is due to redistribution from brain to other tissues and not metabolism. In 1979 Sheiner and coworkers developed a mathematical model linking pharmacokinetic and pharmacodynamic measurements by describing the events following the commencement, and later discontinuation, of a d-tubocurarine (d-TC) infusion in surgical patients.[81]

The closely linked fields of pharmacokinetics and pharmacodynamics, like other disciplines, are continually evolving. New techniques help us better understand the basis of interdrug and interpatient differences in pharmacologic events and to rationally improve drug therapy. In this article we review some of the areas that are providing new insights by using sometimes novel applications of state-of-the-art pharmacokinetic and pharmacodynamic techniques.

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SOME FACTORS INFLUENCING PHARMACOKINETICS AND PHARMACODYNAMICS

Anesthesia

A classic study of the effects of anesthesia on drug uptake and disposition is the work of White et al on the effects of halothane on the pharmacokinetics of ketamine in the rat.[91] Halothane, 0.8 per cent in oxygen, delayed the absorption of intramuscularly administered ketamine as well as delaying the distribution and redistribution of ketamine, whether administered intramuscularly or intravenously, and prolonging its elimination half-life, all presumably as a result of cardiovascular depression. The in vivo metabolism of intravenously administered ketamine was decreased by halothane in a concentration-dependent manner, possibly as a result of depressed cardiac output. In vitro metabolic studies demonstrated a noncompetitive inhibition of ketamine N-demethylation by halothane with 50 per cent inhibition produced by 5.1 per cent halothane. Urinary excretion of two major ketamine metabolites was significantly decreased during halothane anesthesia. The result of the alteration of ketamine pharmacokinetics by halothane was a prolongation of its pharmacologic action.

An elegant sheep model developed by Runciman and colleagues permits the direct measurement of the distribution and elimination of drugs and their metabolites in awake and anesthetized animals.[66] By infusing a marker drug, such as iodohippurate, as well as the drugs of interest, and drawing blood samples simultaneously from catheters placed chronically in arteries supplying and veins draining various key organs or tissues (Fig. 1), the investigators are able to measure blood flow through and drug concentration gradients across those or-

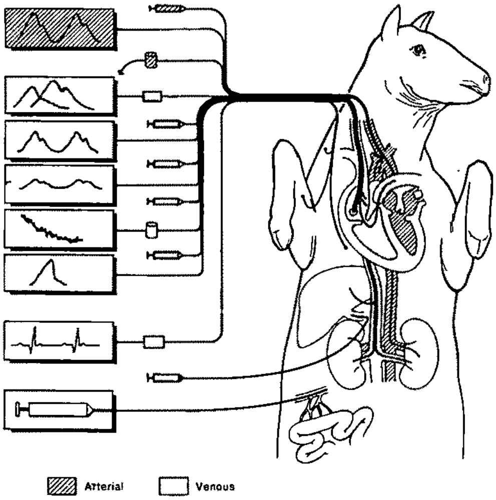

Figure 1. An illustration of the positions of some of the catheters chronically placed in sheep for drug infusions and arterial and venous blood sampling in the studies of the effects of anesthesia on blood flow and drug disposition.[54,66,68] (*From* Runciman WB, Isley AH, Mather LE, et al: A sheep preparation for studying interactions between blood flow and drug disposition. I: Physiological profile. Br J Anaesth 56:1015–1028, 1984; with permission.)

gans and tissues from moment to moment and day to day in awake and anesthetized animals.

Runciman and associates used the sheep model to study the effects of general anesthesia and spinal anesthesia on the disposition of cefoxitin, a broad spectrum semisynthetic antibiotic, the renal clearance of which is dependent on both renal blood flow and tubular secretion.[68] General anesthesia with 1.5 per cent halothane significantly decreased renal blood flow and decreased both the renal cefoxitin extraction ratio and clearance over 50 per cent, resulting in a 2.5- to 5.0-fold increase in arterial cefoxitin concentrations. High thoracic subarachnoid anesthesia with the local anesthetic amethocaine had no measurable effect on either renal blood flow or the clearance of cefoxitin.

The disposition of meperidine, which is eliminated primarily by hepatic metabolism, was studied in the sheep model by Mather et al.[54] Because the hepatic extraction ratio of meperidine is nearly one in the sheep, the approximately 50 per cent reduction in hepatic blood flow by 1.5 per cent halothane caused an equivalent reduction in the elimination clearance of meperidine, with no change in its hepatic extraction ratio, and a doubling of arterial meperidine concentrations. Subarachnoid anesthesia had no effect on the disposition of meperidine in the sheep.

Halothane (2.0 MAC, 1.74 per cent in oxygen) anesthesia in the dog has been reported to cause a decrease in the elimination clearance of propranolol through a direct inhibition of hepatic drug metabolism rather than through an effect on liver blood flow.[63] In a similar animal preparation, halothane (1.74 per cent) was shown to increase the arterial/venous propranolol concentration ratio across the hind limb of the dog, suggesting halothane alters drug distribution as well as elimination clearance.[38]

Although the effects of anesthesia on the disposition of drugs are not thoroughly studied in man, there are certainly suggestions that anesthetic agents may affect elimination clearance of high hepatic extraction ratio drugs.[32,33,85] Altered elimination clearance by potent inhalation anesthetics may have important implications for drugs used concomitantly with those agents or when using the pharmacokinetics of drugs administered during inhalation anesthesia to design infusion regimens for use in total intravenous anesthesia. The interested reader is referred to the extensive review of the literature on the effects of anesthesia on the disposition of drugs published recently by Runciman and Mather.[67] One should also bear in mind that other perioperative physiologic perturbations, such as cardiopulmonary bypass, may affect both the pharmacokinetics[41] and the pharmacodynamics[6] of drugs.

Age

The elderly tend to be more reactive to standard doses of many intravenously administered anesthetic agents including thiopental,[14,19,22,42] etomidate,[3] propofol,[24] diazepam,[37] midazolam,[21,36] morphine,[69] meperidine,[53] fentanyl,[75] and alfentanil.[75] The increased sensitivity of the elderly to these agents is due to age-related pharmacokinetic or pharmacodynamic changes.

Pharmacokinetic changes known to occur with age include changes in total volume of distribution, the direction and extent of which depend on the lipophilicity of the drug, and reductions in elimination clearance.[70,71] Age-related changes in the volume of distribution are due to a decrease in both the proportion of body weight represented by total body water and the lean body mass with age.[12] An age-related decrease in cardiac output occurs with a concomitant alteration in the distribution of systemic blood flow, usually at the expense of drug-eliminating organs.[9] (More recent evidence suggests that such age-related changes in cardiac output are not seen when only healthy elderly are considered.[65]) Renal function decreases with age,[16] resulting in an unexpected intensity or duration of drug effect in the elderly when they are given standard doses as part of a multiple dose or continuous infusion regimen. Except for recommendations that dosage of renally cleared drugs be adjusted to the age-related decrease in renal function, these kinetic changes with age offer no guidelines for improving drug therapy in elderly patients.

Changes in total volume of distribution and elimination clearance with age can affect the elimination half-lives of drugs but cannot explain the exaggerated responses of the elderly to standard doses of intravenously administered drugs with a rapid onset of effect.

Several studies have attempted to establish the pharmacokinetic or pharmacodynamic basis of the increased reactivity of the elderly to thiopental.

There appear to be no pharmacodynamic differences between young and elderly patients. Christensen et al reported that plasma thiopental concentrations associated with the onset of hypnosis in young and old patients were not different despite lower induction doses in the elderly.[15] In addition, Homer and Stanski found no difference between young and old patients in the relationship between estimated steady-state plasma thiopental concentrations and the frequency below which 95 per cent of the EEG power lies.[42]

There are several conflicting reports regarding age-related differences in thiopental pharmacokinetics. Jung et al describe a correlation between age and the total volume of distribution of thiopental, but the investigators found no change in its early distribution and so could not explain the reduced induction dose requirement in the elderly.[44] Christensen and colleagues found not only an age-related decrease in the volume of distribution in the elderly but also a decrease in the rate of drug transfer from their central compartment to their fast compartment.[15] Homer and Stanski have reported a marked decrease in the initial distribution volume of thiopental with age, which results in less initial dilution of a dose of thiopental in the elderly.[42] Because thiopental equilibration between blood and brain is very rapid,[61] either a slower rate of transfer of the drug from the central to the fast compartment[15] or a decrease in the volume of its central compartment[42] would offer satisfactory explanations of the increased central nervous system and cardiovascular sensitivity of the elderly to standard doses of thiopental. However, the decrease in the central volume of thiopental with age could not be demonstrated in a recent study.[39,47] In addition, these authors suggest that the increased reactivity of the elderly to thiopental may be due to pharmacokinetic changes occurring before the drug is mixed within the initial distribution volume of the traditional three-compartment pharmacokinetic model.[39,47] Alternatively, the age-related increased sensitivity to thiopental may be due to pharmacodynamic changes that are not detectable with current techniques.

Scott and Stanski studied the decreased dose requirements of both fentanyl and alfentanil with age.[75] They could find no age-related changes in the pharmacokinetic variables describing the disposition of either drug. However, the sensitivity of the brain to both drugs, measured by the spectral edge frequency of the EEG, did increase with age. The authors speculate that the age-related changes in the pharmacodynamic response to fentanyl and alfentanil may be due to changes in the opiate receptor.

Pharmacogenetics

Anesthesiologists are keenly aware of the importance of pharmacogenetic variability through their familiarity with diminished pseudocholinesterase activity. The fact that measured plasma pseudocholinesterase concentrations are normal when a qualitative measure, such as the dibucaine number, is abnormally low indicates that an individual has a genetically determined atypical pseudocholinesterase. Such patients have reduced capacity to metabolize succinylcholine and thus greatly prolonged neuromuscular block may be seen following administration of standard doses.[58]

During the past 10 years pharmacogenetic variability of hepatic P-450 enzymes have been shown to affect the metabolism of a large number of drugs. Independent investigators in the United Kingdom[50,84] found a bimodal distribution of the ability to metabolize an antihypertensive drug, debrisoquine, with approximately 5 per cent of the population having limited capacity to hydroxylate this drug. It was these patients who were most likely to suffer side-effects (for example, orthostatic hypotension) on standard therapy. Family studies later indicated that this defect was monogenically controlled, probably at an autosomal recessive site.[62] At about this same time, investigators in Germany found that the ability to oxidize sparteine was similarly biomodally distributed.[28] The metabolism of sparteine and debrisoquine were later shown to be coregulated.[10] Figure 2 illustrates a loglinear bimodal distribution of phenotypes for this metabolic pathway. These studies paved the way for several series of crossover studies in which individuals of known abilities to metabolize debrisoquine are given a new drug of interest. These crossover studies have established that many drugs (especially beta-blockers and tricyclic antidepressants), which are oxidatively metabolized, are

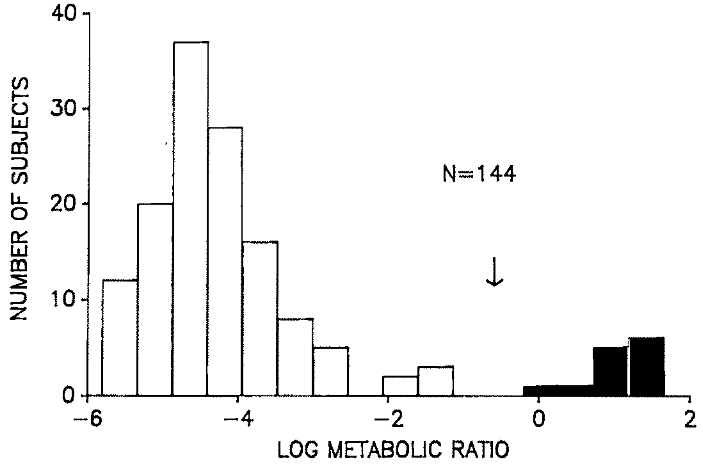

Figure 2. Frequency distribution histogram of dextromethorphan O-demethylation in a Spanish population (unpublished preliminary data). The arrow indicates the proposed antimode (log 0.3 = −0.52) between the Gaussian distributions of poor and extensive metabolizer phenotypes. The O-demethylation of this drug appears to be coregulated by the polymorphic debrisoquin hydroxylase enzyme.

more slowly metabolized in patients having the so-called poor debrisoquine hydroxylator phenotype.[27] The resultant decrease in elimination clearance makes these patients more likely to have prolonged durations of action and elevated steady-state concentrations, which may be associated with exaggerated or adverse effects.

To date no drug used commonly by anesthesioloists has been shown to have genetic polymorphism of oxidative metabolism. Suggestive evidence indicates that some drugs deserve further investigation. Dundee reported prolonged elimination half-lives of midazolam in 14 of 217 patients given the drug prior to surgery.[20] Based on this observation, Klotz performed a crossover study in which midazolam clearance was measured in subjects having a wide range of sparteine oxidation phenotypes and no correlation was seen.[46] However, the authors mentioned that earlier in vitro data[43] both corroborated their negative in vivo crossover data and suggested that a recently elucidated polymorphic P-450 isozyme (that is, the so-called mephenytoin hydroxylase enzyme[89]) may explain the high concentrations seen by Dundee. Similarly, in vitro[40] and in vivo[56] data provide preliminary evidence that observations of slow metabolic clearance of alfentanil in approximately 5 per cent of healthy patients[55,77] may be explained on the basis of the debrisoquine hydroxylase isozyme. Further in vivo studies are needed to clarify whether the oxidative metabolism of midazolam, alfentanil, or other drugs is mediated by a genetically variable P-450 enzyme.

Stereoisomers

Many drugs have chemical structures that contain at least one asymmetric carbon atom, resulting in stereoisomerism, that is, two nonsuperimposable mirror-image species referred to as the *dextro* and *levo* forms of the molecule. These forms are similar chemically, thus standard methods of chemical separation and detection (for example, chromatography) and synthesis (for example, drug production) will not discriminate between the isomers. However, because of the stereospecificity of enzymatic and receptor processes, stereoisomers are not necessarily equivalent pharmacokinetically or pharmacodynamically. In anesthesia the barbiturates[2] and ketamine[90] are enantiomeric drugs.

Since most enantiomeric drugs are marketed as racemic mixtures (that is, they contain equal amounts of all stereoisomers), both practical and theoretical problems can arise. As is the case with ketamine, one isomer may be responsible for the bulk of the unwanted (in the case of ketamine, psychic) side-effects of the drug.[90] Though ketamine is somewhat atypical in that it appears there is no difference in disposition between the two isomers,[92] there are, as expected, differences in potency among d-, l-, and racemic formulations.[72] It has been argued that if a formulation containing just d-ketamine was available, it would be a more useful drug.[31]

A further problem is that most pharmacokinetic and pharmacodynamic studies are performed without determining the proportion of the isomers present at the times of plasma drug concentration or effect measurements; as isomers often have differing rates of metabolism or excretion, the proportion of d and l forms in blood samples will vary with time. An example of the complexity presented by racemic drug mixtures is illustrated in Figure 3. In this study Echizen et al found that the plasma concentration versus effect relationship varied depending on whether racemic verapamil was administered orally or

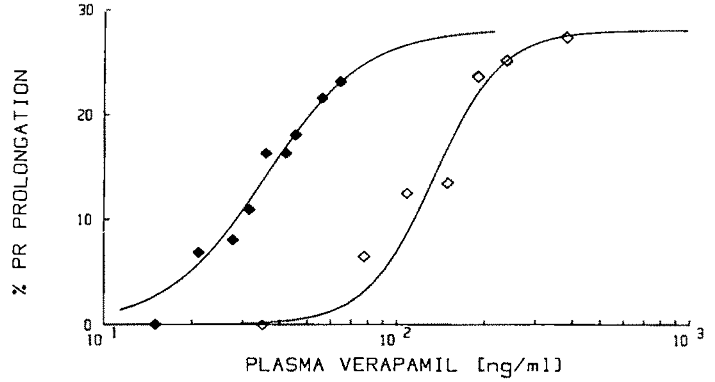

Figure 3. Plasma concentration-response curves of P-R prolongation after administration of 10 mg intravenous (*closed diamonds*) and 160 mg oral (*open diamonds*) racemic verapamil. Although the maximal effects are the same, the EC50 reflects a more than threefold difference in potency. (*From* Echizen H, Vogelgesang B, Eichelbaum M: Effects of d, l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. Clin Pharmacol Ther 38:71–76, 1985; with permission.)

intravenously.[26] As the more potent l isomer is preferentially metabolized, the addition of the first-pass metabolism following oral administration accentuated differences in isomeric composition in subsequently collected plasma samples.

One must be very careful when interpreting data from studies of entantiomeric drugs.[4,18] New methods of separation using chiral chromatographic columns have made it possible to measure the concentration of each isomer.[83] Future studies making use of these techniques might shed new light on some old questions.

POPULATION PHARMACOKINETICS

Optimal safe and effective individual drug administration regimens require knowledge of the effective drug concentration, the pharmacokinetics of the drug, the variability of the pharmacokinetics, and contributions to the variability by identifiable factors. There are several ways to estimate these last three and arrive at a description of the population pharmacokinetics. Beal and Sheiner have recently described in detail two of the most common approaches to estimating population pharmacokinetics, which they call the standard two-stage method (STS) and the first order method (FO).[8]

The STS method of estimating population pharmacokinetics is, as the name suggests, the method with which many are familiar. At the first stage individual pharmacokinetic models for a given drug are described for a relatively small number of subjects. In the second stage average pharmacokinetic variables are calculated from those of the individual models along with an estimate of the data dispersion. Correlations of the individual kinetic parameters with such factors as age, weight, sex, etc. may also be sought directly or indirectly. The STS method requires a large number of blood samples obtained at critical times and, while useful, may not provide the best estimate of the population kinetics and, therefore, will provide less than optimal guidance in the use of the drug of interest.

The FO method of estimating population pharmacokinetics is a relatively new method developed and implemented in the NONMEM program by Beal and Sheiner.[7] The FO method pools the plasma concentration versus time data for a given drug from a relatively large number of individuals along with various patient characteristics to produce a single kinetic model with a realistic estimate of not only intrasubject variability but also intersubject variability and the contributions of patient characteristics to that variability. Because the analysis is performed on pooled data from a large number of subjects, relatively little data from each subject is needed. However, the FO analysis is more complex than is the STS analysis.

Maitre and associates recently reported estimates of the population kinetics of alfentanil based on the FO method.[52] They used the NONMEM program to analyze pooled data of 45 patients in five groups of 5 to 15 patients from four previously published studies. Half of the pooled data, 307 plasma alfentanil-time points, were randomly chosen and used to construct the population kinetic model. The influence of age, body weight, sex, anesthetic duration, and use of etomidate and/or inhalational agents on interindividual variability was also determined. Elimination clearance (Cl_E) and K_{31} decreased approximately 1 per cent per year after the age of 40. Body weight did not affect Cl_E but it did influence the initial volume of distribution, V_C. The mass normalized V_C was 15 per cent larger in females. Unexplained interindividual differences in the plasma alfentanil versus time profile were described by assigning the variability to Cl_E (48 percent) and V_C (33 percent). The residual intraindividual variability was 25 per cent. When the second half of the data was analyzed with the parameters other than residual variance constrained to their estimated values, the residual variability estimate was essentially the same as that of the first analysis. The same group of investigators then used the NONMEM results to predict the plasma alfentanil concentration versus time relationship in 19 patients to whom alfentanil was administered by a variable bolus and infusion regimen.[51] The average difference between the 598 predicted and measured plasma concentrations (that is, the mean bias) was not different from zero. This suggests that the FO population kinetic estimates for alfentanil will be quite useful for designing infusion regimens.

PHARMACOKINETIC-PHARMACODYNAMIC MODELS

Patients can vary widely in their responses to a dose of drug. Such variability may result from differences in what the drug does to the patient (pharmacodynamics) or in what the body does with the drug (pharmacokinetics). Before meaningful quantitation of differences in dose-response relations can be undertaken, it is necessary to discern the relative importance of both kinetic and dynamic variability. Traditionally, pharmacokinetics are best studied in circumstances that maximize the changes in concentration with time (that is, following rapid intravenous administration) whereas pharmacodynamics are best studied by relating steady-state concentrations (that is, during continuous intravenous infusion) with the measured effect. As these study designs are at cross purposes, it has been necessary to study kinetics and dynamics on separate occasions. Furthermore, because the attainment of steady-state plasma concentrations is time-consuming, good concentration-effect data, particularly in unsteady clinical settings, are difficult to obtain. Advances in clinical pharmacokinetics now allow for meaningful analysis of concentration-response data in non-steady-state conditions (for example, following a rapid intravenous injection). This is accomplished by using combined pharmacokinetic-pharmacodynamic models with separate "effect compartments" to kinetically define drug concentration-response relations. These analyses are actually best done following a rapid intravenous injection because a well-founded mathematical description of drug disposition facilitates this sort of analysis.

Fundamental to the understanding of combined pharmacokinetic-pharmacodynamic models is the dose-response relationship. Response can be measured as the maximum effect seen at any time following drug administration or as the effect seen at an arbitrary time following administration. However, interindividual variability in drug absorption and disposition may affect the magnitude of drug effect observed with either of these schemes. Two kinds of responses can be observed in dose-response studies, quantal or graded, depending on the nature of the effect produced by a drug.

Quantal responses are described by all-or-none data regarding the presence or absence of a state, such as sleep or analgesia, after administration of a drug. The variable frequency of response to doses of a given drug may be normally distributed or skewed. By plotting the logarithm of dose against the number of subjects responding, a skewed distribution becomes log-normal. This normal or log-normal distribution, if plotted as cumulative response (that is, percentage responding to a given dose), has the classic sigmoid shape (Fig. 4). The median effective dose (ED50) provides information on the position of the curve along the dose axis but provides none about the shape of the curve, that is, its slope. In anesthesia, MAC is the most familiar example of an ED50 of such a quantal dose-response relationship.

Graded responses (for example, per cent paralysis resulting from

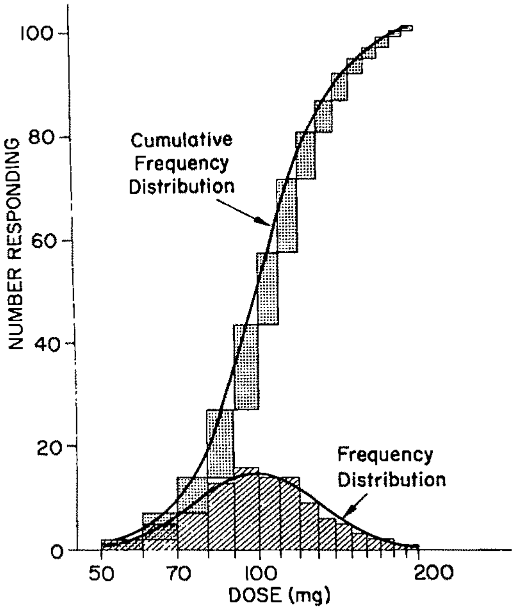

Figure 4. Schematized graph demonstrating the association between a log-normal frequency distribution (note the abscissa is log-scale) and the sigmoid-shaped cumulative frequency distribution. (*From* Ross EM, Gilman AG: Pharmacodynamics: Mechanisms of drug action and the relationship between drug concentration and effect. *In* Gilman et al (eds): Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7th ed. New York, Macmillan, 1985; with permission.)

neuromuscular blockers) are measured on a continuous scale ranging from no effect to maximum effect and are proportional to receptor occupancy. When responses are plotted as a function of dose, the curve is a rectangular hyperbola, linear for the lowest doses and least effects, which are usually of little clinical interest. Plotting the effect as a function of log-dose yields the classical sigmoid curve that is linear from 20 to 80 per cent of maximum effect (Fig. 5).

Wagner[86] has proposed that these types of relations be expressed mathematically by an equation described by Hill:

$$E = \frac{D^{\gamma}}{D^{\gamma} + D(50)^{\gamma}} \tag{1}$$

where E is the intensity of pharmacologic effect (or cumulative percentage of quantal response), D is the dose related to that effect, D(50) is a constant giving the dose at 50 per cent effect, and γ is a parameter giving slope and sigmoidicity. When graded responses are considered, a variation of equation 1 is used:

$$E = \frac{E_{max} \times D^{\gamma}}{D^{\gamma} + D(50)^{\gamma}} \tag{2}$$

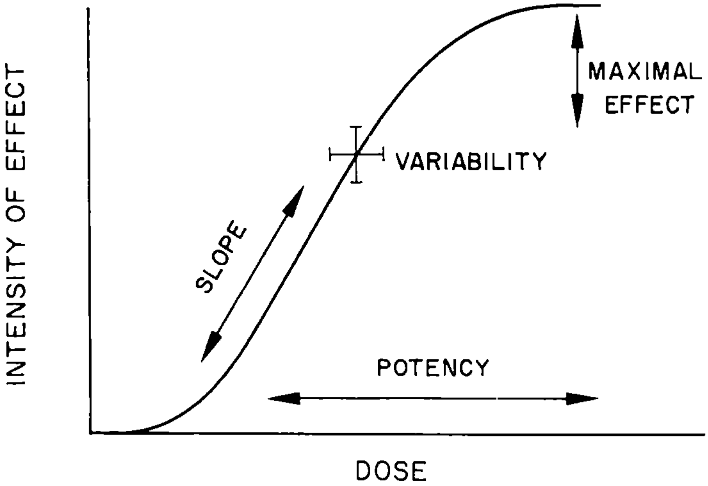

Figure 5. Schematized graded dose-response curve indicating the important features. The slope is the expression of the relation between incremental changes in dose and effect. The intensity of effect plateaus at an upper range of dose, thus attaining a maximal effect. A drug's efficacy is related to this value. Potency is related only to the position of the dose-response curve along the abscissa; it is not related to the slope or maximal effect. In clinical pharmacology, one should always anticipate the presence of interindividual variability for all of these variables. (*From* Ross EM, Gilman AG: Pharmacodynamics: Mechanisms of drug action and the relationship between drug concentration and effect. *In* Gilman et al (eds): Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7th ed. New York, Macmillan, 1985; with permission.)

where E_{max} is the maximum effect. When γ is unity, the so-called E_{max} effect model is observed. Important requisites when these equations are used to describe dose-response data are that the effect measured is truly a measure (and, optimally, a direct one) of the pharmacologic effect of the drug being studied and that the observed maximum effect is truly the maximum effect. That is, for example, in experiments in which the dose or concentration is varied over such a small range that the observed effects only fall between 20 and 80 per cent of the maximum effect, a linear or proportional model may be more appropriate (see following).

As several pharmacokinetic processes may affect the concentration of drug at the effector organ following dose administration, the effect of pharmacokinetic variability can be minimized by examining plasma concentration-response rather than dose-response relations. The branch of clinical pharmacology concerned with therapeutic drug monitoring is largely based on this principle. Traditionally, the plasma concentration-response relation is established by correlating plasma concentrations at steady-state with measurements of pharmacologic response. One assumes that plasma concentration is in equilibrium with tissues at the site of action (the biophase) when distribution processes are at steady-state. In order to meet the conditions of this assumption, infusions or intermittent doses are continued to steady-state. This permits study of only a few points on the concentration-response curve for many drugs because of the time required to achieve multiple steady-states in an individual. Recently, sophisticated infusion pumps with the ability to continuously alter the infusion rate based on the disposition of the drug of interest (see following) have permitted simulation of steady-state conditions so that multiple points on the concentration-response curve can be studied in a single individual. Bührer and colleagues[13] achieved a reasonable approximation of steady-state for thiopental in as short as 3 to 5 minutes for the purpose of correlating plasma concentrations with EEG changes (Fig. 6).

Ausems et al[5] studied the relation between plasma alfentanil concentrations and the presence or absence of response to painful surgical stimuli. They argued that alfentanil's unusually rapid equilibration between plasma and the effector-site in brain tissue (see following) made examination of these data valid in the absence of steady-state conditions. A variation of equation 1 was used in which the clinical state of responsive or nonresponsive was related to alfentanil concentrations:

$$\text{Probability of no response} = \frac{[A]p^{\gamma}}{[A]p_{50}{}^{\gamma} + [A]p^{\gamma}} \qquad (3)$$

where [A]p is alfentanil plasma concentration, $[A]p_{50}$ is the alfentanil concentration that results in a 50 per cent probability of a response,

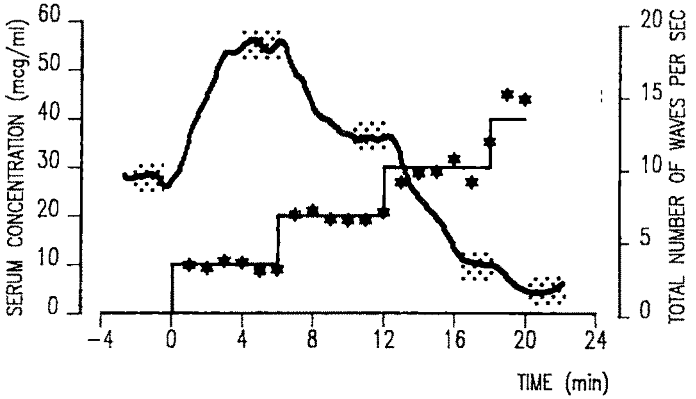

Figure 6. Target and measured serum thiopental concentrations compared with the resulting EEG effect in a human subject. Rising from time zero is the calculated line of step-change to plateau serum concentrations to be produced by the constantly varied rate infusion. The solid circles represent the actual measured serum thiopental concentrations. The other solid line is the continuously measured effect of thiopental on the EEG. In this instance, aperiodic analysis yielding "total number of waves per second" was used to describe the EEG. Each plateau of serum thiopental concentration is associated with a distinct EEG effect. (*From* Bührer M, Maitre PO, Ebling WF, et al: Defining thiopental's steady-state plasma concentration-EEG effect relationship. Anesthesiology 67:A399, 1987; with permission.)

and γ is defined as in equation 1. The investigators were able to construct concentration-response (probability) curves (Fig. 7) for a variety of events (that is, intubation, skin incision, skin closure, and spontaneous ventilation) in addition to individual patient and mean curves for the intraoperative periods for breast, lower abdominal, and upper abdominal surgeries. The authors felt that this method produced compelling enough results to allow them to confidently recommend that alfentanil infusions be titrated throughout operation according to the responses of each patient.

During most clinical circumstances in anesthesia we deal with non-steady-state conditions. Thus, it becomes important to understand the temporal relation or lag between plasma concentrations and pharmacologic effect. Pharmacokinetic analysis of blood or plasma washout curves yields several phases or compartments. The concentrations in these peripheral compartments are driven by and follow the concentration changes in the plasma. Levy first proposed that concentrations in one of these peripheral compartments might have the same temporal courses as that of the observed effect.[49] When concentration is plotted as the independent variable against effect, one may encounter clockwise or counterclockwise hysteresis. In the case of counterclockwise hysteresis, concentrations rise before effects are observed and concentrations fall before the effect dissipates. The exact opposite relationships are observed in clockwise hysteresis. If no or minimal hysteresis is seen, then the pharmacokinetic compart-

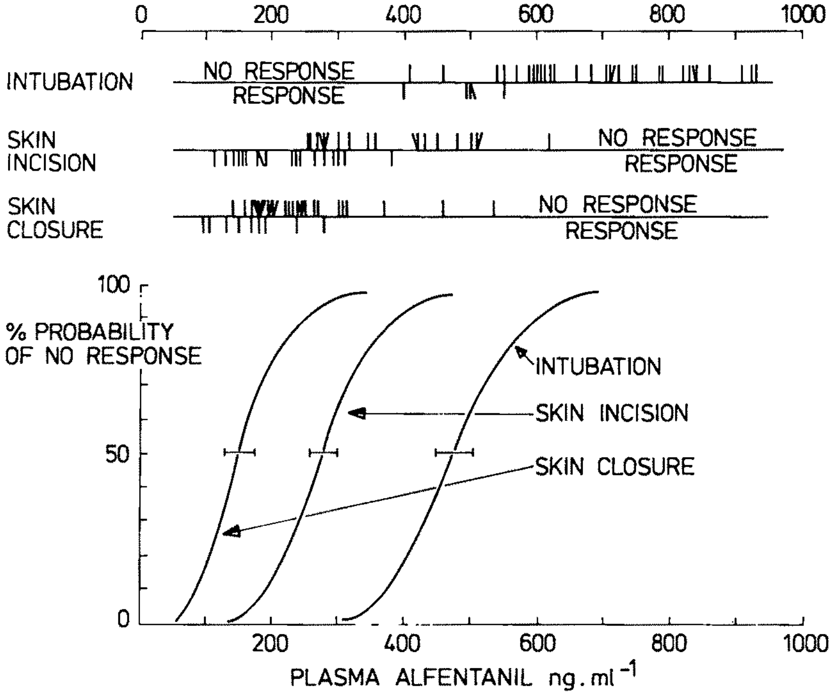

Figure 7. Quantal data of response at varying plasma alfentanil concentrations and the corresponding concentration-response curves. During various events (intubation, skin incision, skin closure) patients were noted to respond or not respond to the stimulus (tic marks below or above the lines, respectively). The position along the line corresponds to the measured plasma alfentanil concentrations (abscissa) at the time of the event. The graphs below represent the calculated relations between plasma alfentanil concentration and the likelihood of observing no response to the stimulus. Also shown on these curves are the 95 per cent confidence limits of the concentrations at a 50:50 likelihood. (*From* Ausems ME, Hug CC, Jr., Stanski DR, et al: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. Anesthesiology 65:362–373, 1986; with permission.)

ment and the effect compartment share the same time course and, perhaps, the same tissue site. Because the actual mass of drug-specific tissue for a given effect of a drug is usually quite small compared with the vast mass of nonspecific tissue, the contribution of the effector-site to the disposition of systemically administered drug is inconsequential. Therefore, if a strong temporal correlation between the pharmacologic effects and concentrations in a kinetic compartment exists, it is probably serendipitous.

An alternative approach proposed by Segre[76] and adopted by Sheiner[81] is shown schematically in Figure 8 and models response as a function of the drug concentration in a biophase compartment. The kinetics of the biophase are related to the central compartment by a first order process (that is, drug reaches the biophase along a single concentration gradient). This effect compartment is also assumed not

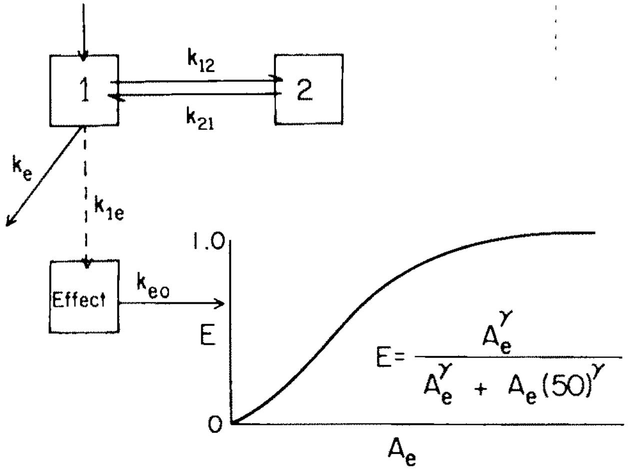

Figure 8. Multicompartmental system used to model the distribution and elimination of drug (dTc) and its effects (twitch height suppression). D-tubocurarine injected into the central compartment distributes to one (in this example) or more tissue compartments, as determined by the transfer rate constants, while also being cleared from the body. The square marked "effect" represents the biophase of dTc effect. The rate constants k_{1e} and k_{eo} determine the rate of onset and offset of the effect. The sigmoidal plasma concentration-effect relation (at steady state) can be calculated from these variables and the so-called Hill equation (eq. 1). (*From* Stanski DR, Ham J, Miller RD, et al: Pharmacokinetics and pharmacodynamics of d-tubocurarine during nitrous oxide-narcotic and halothane anesthesia in man. Anesthesiology 51:235–241, 1979; with permission.)

to alter the pharmacokinetic properties of the drug and is linked to the measured effect by equation 1 with biophase concentrations substituted for dose. The plasma concentrations and the observed effects can thus be tracked separately as demonstrated in Figure 9. This approach allows calculation of steady-state plasma concentration-response relations for multiple points in an individual following a single dose and estimation of the Cpss(50) or the concentration at steady-state that would produce 50 per cent of the maximum effect. The rate constant exiting the effect compartment characterizes the time course of drug equilibration with the site of action and is often expressed as $t_{1/2}k_{eo}$. An additional consideration when using the combined pharmacokinetic-pharmacodynamic model following a single dose is the ability to measure the effect in a short time relative to the changes in plasma drug concentration. For example, determining the slope of $PaCO_2$ versus minute ventilation curve would be inappropriate when plasma drug levels are changing rapidly but measuring twitch suppression following a bolus of pancuronium would be ideal.

Data analysis for the combined pharmacokinetic-pharmacodynamic model follows the ensuing general scheme. First, pharmacokinetic data are fit to an appropriate exponential decay curve that can be expressed in terms of a compartmental model. These terms are

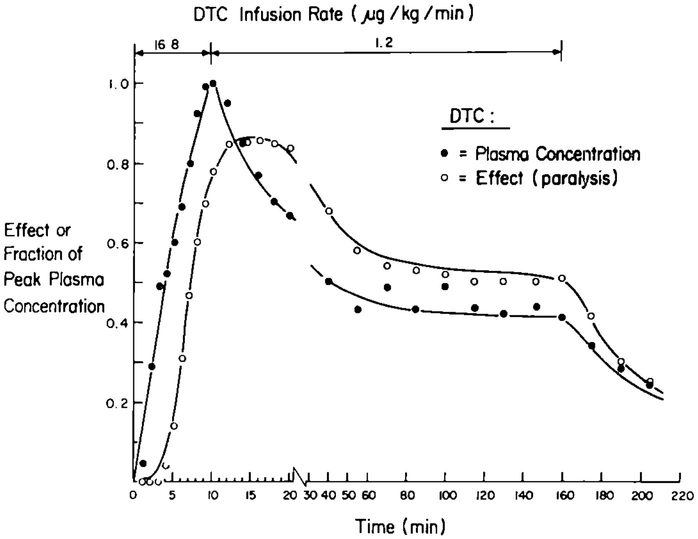

Figure 9. Kinetic analysis of plasma dTc concentrations (*closed circles*) and twitch height suppression (*open circles*) in a patient. The solid lines are least squares fits of the observed values indicated by the data points. (*From* Stanski DR, Ham J, Miller RD, et al: Pharmacokinetics and pharmacodynamics of d-tubocurarine during nitrous oxide-narcotic and halothane anesthesia in man. Anesthesiology 51:235–241, 1979; with permission.)

fixed and serve as an input function for the effect model. A biophase compartment is then added to the model with first order rate constants adjusted to permit an optimal time course of concentrations for the observed effects, which are linked to this compartment by the Hill equation. Ideally, the biophase compartment should be mathematically expressed in such a manner that no actual net transfer of drug occurs, lest the pharmacokinetics be altered.

Because not all experiments possess enough data to characterize a full sigmoid curve, Fuseau and Sheiner have proposed a nonparametric pharmacodynamic model that is similar to this description except that it does not presuppose the Hill equation for data analysis.[35] Along these lines, Eudeikis et al used a simple linear relation between concentration and response in their model because it appeared all concentrations were between levels producing 20 and 80 per cent of maximum effect.[29]

It is rarely possible to attach physiologic significance to Cpss(50) measurements of this type. However, d'Hollander and Delcroix derived values for Cpss(50) determined under clinical circumstances[17] that were similar to those of Waud and associates[87,88] for the analogous equilibrium constant between drug and receptor in mammalian striated muscle. A study of the antifibrinolytic effects of epislon-aminocaproic acid (EACA) also supported the validity of this approach; it was found that the Cpss(50) agreed with the equilibration constant of the EACA-plasminogen complex.[34]

As interindividual differences in effect following drug administration can be due to either pharmacokinetic or pharmacodynamic factors, the most expeditious means of discerning which are the important elements would be a study that measures drug concentrations as well as effect and analyzes these data with the combined approach. Stanski and colleagues have used combined pharmacokinetic-pharmacodynamic models to demonstrate that a pharmacodynamic rather than a pharmacokinetic interaction increases sensitivity to d-tubocurare under halothane anesthesia.[82] Fisher, using similar models, showed that dosing adjustments for single injections of d-tubocurare are unnecessary in infants because of offsetting differences in distribution volume and Cpss(50) when compared with older children and adults.[30]

Homer and Stanski[42] and Arden et al[3] used the combined pharmacokinetic-pharmacodynamic technique to study the increased reactivity of the elderly to thiopental and etomidate, respectively; they conclude that the elderly are more sensitive to these drugs because of age-related kinetic rather than dynamic changes. Dundee[23] recently presented further evidence of the increased sensitivity of the elderly to thiopental, but work done by Henthorn et al[39] and Krejcie et al[47] question the clear distinction of the kinetic differences seen in the earlier study.[42] Additionally, Bührer and colleagues found improved EEG techniques that enabled them to more accurately delineate the cerebral effects of thiopental on the EEG, including the biphasic response.[13] It is anticipated that, with improvements in pharmacokinetic study design and analysis, as well as in measurement of cerebral effect, a clearer image will emerge of the factors that make the elderly more reactive to intravenous anesthetics. This is important because it is likely that conditions associated with age, rather than age itself, are at least partially responsible and it would be useful to be able to better identify these factors so that dosing adjustments could be more rationally based.

Combined pharmacokinetic-pharmacodynamic models were used by Scott et al to examine differences between fentanyl and alfentanil.[74] Their study clearly demonstrated that alfentanil equilibrates more rapidly between blood and the central nervous tissue biophase than fentanyl, with $t_{1/2}k_{eo}$s of 1.1 minutes and 6.4 minutes, respectively. This difference is shown graphically in Figure 10. With this information they were also able to address the discrepancy between potency ratios reported between bolus doses (alfentanil is three to ten times less potent) and steady-state concentrations (alfentanil is 40 to 75 times less potent). It was reasoned that bolus dose and steady-state infusion potency ratios would be similar only if the $t_{1/2}k_{eo}$s and the initial volumes of distribution (V_C) were the same for the two drugs. Fentanyl's V_C was five times larger and its $t_{1/2}k_{eo}$ was also about five times larger, thus explaining the difference in the potency ratios. Other aspects of the concentration-response relations were, as might be expected, similar. The E_{max} for EEG changes were the same for alfentanil and fentanyl as were the γ values describing a steep concentration-response relationship.

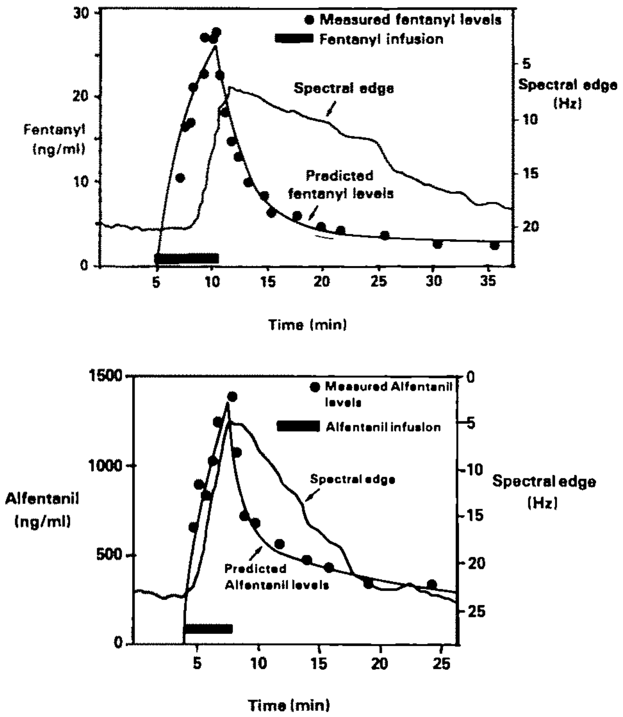

Figure 10. Kinetic analysis of plasma fentanyl (*solid circles, left panel*) and alfentanil (*solid circles, right panel*) with continuous measure of leading spectral edge from the processed EEG. The solid lines through the plasma concentration data are least squares fits. The drug infusion rates are indicated by the solid bars and were 150 μg/min for fentanyl and 1500 μg/min for alfentanil. Note the discrete lag of the spectral edge changes behind the serum concentrations of fentanyl and the near absence of such a lag with alfentanil. (*From* Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234–241, 1985; with permission.)

INTRAVENOUS DRUG INFUSIONS

It is becoming increasingly necessary or desirable for the anesthesiologist to administer drugs by continuous intravenous infusion. There are many possible approaches to infusions, each with its advantages and disadvantages.

A basic principle of drug infusions is that the steady-state plasma drug concentration acheived as the result of a continuous, constant rate infusion of sufficient duration (C_{SS}) is equal to the ratio of the infusion rate (I) to the elimination clearance (CL_E):

$$C_{SS} = I/CL_E \qquad (4)$$

However, if only a continuous, constant rate infusion is used, the time necessary to attain the desired plasma drug concentration at or near the steady-state concentration will be painfully long. An infusion lasting one half-life of the drug being infused will produce plasma drug concentrations that are approximately half of the eventual steady-state concentration. An infusion lasting two half-lives will produce concentrations that are nearly 50 per cent closer to the steady-state concentration, or three quarters of it. Ninety per cent of the steady-state concentration is achieved only after a continuous, constant rate infusion administered for more than three half-lives of the drug being infused. Clearly, infusing a drug in this manner is not suitable to the needs of the anesthesiologist who needs both to achieve effective plasma concentrations rapidly and maintain them continually while avoiding both side-effects and prolonged post infusion drug action.

During the time required to reach steady-state drug concentrations by continuous, constant rate infusions, the drug not only is being cleared from the body but is also being distributed throughout it. Until the drug in the tissues of the body are in equilibrium with that in the blood (that is, until steady-state is achieved) the drug distribution processes in effect dilute the drug, producing plasma concentrations that are lower than those achieved at steady-state. There are several ways to infuse drugs in such a way as to achieve and maintain effective drug concentrations during distribution as well as after it.

The simplest way to accomplish this is to use the combined bolus and infusion method of Mitenko and Ogilvie.[59] The bolus or loading dose is chosen as though it would provide effective plasma drug concentrations upon instantaneous mixing and equilibration throughout its entire volume of distribution, $V_{D\beta}$ (that is, the body):

$$\text{Dose} = C_{SS} \cdot V_{D\beta} \tag{5}$$

This is administered simultaneously with the commencement of an infusion matched to elimination clearance (by rearrangement of equation 4):

$$I = C_{SS} \cdot CL_E \tag{6}$$

As illustrated in Figure 11, this method effectively produces and maintains effective plasma concentrations from soon after drug administration is begun until the infusion is terminated. However, because drug is not instantaneously distributed throughout the body, this method produces very high initial drug concentrations that persist until distribution is well under way. Thus, an infusion regimen based on the method of Mitenko and Ogilivie[59] is suitable only for drugs, such as muscle relaxants,[79] which, in the hands of the anesthesiologist, have high margins of safety.

The goal of an infusion regimen for a drug of low margin of safety is to minimize initial plasma concentrations while maintaining effective concentrations throughout the infusion, including the distributive phase. This can be accomplished by choosing the loading dose to provide effective plasma concentrations in an initial, rapidly mixing volume of distribution. An intermediate infusion is then commenced

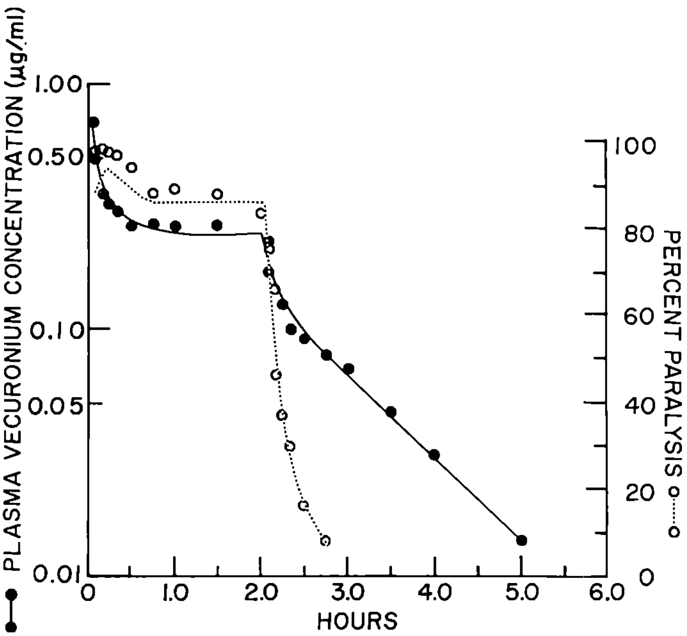

Figure 11. The plasma vecuronium concentration versus time relationship and corresponding per cent paralysis during and after an infusion of the drug[80] using the bolus and infusion method of Mitenko and Ogilvie.[59] (This is a previously unpublished figure from the study of Shanks et al[80] and is reproduced with the kind permission of Colin A. Shanks, MD.)

that will not only match elimination clearance but also compensate for drug loss from the central to the peripheral compartments during the period of extensive drug distribution. The terminal infusion is then matched to elimination clearance as before (equation 6).

Such an approach is illustrated by the etomidate infusion designed to produce hypnosis as part of a totally intravenous anesthesia regimen (Fig. 12).[32] Estimates of both the effective plasma drug concentration and the pharmacokinetic variables describing the multicompartmental disposition of etomidate were used to simulate various infusion regimens until one was obtained that met both the requirements outlined in the preceding paragraph and that of having the patients awaken within 10 minutes of terminating the infusion regardless of its duration. Such an infusion is both effective and easy to use.

In 1968 Krüger-Thiemer proposed the use of ideal drug infusion regimens to rapidly achieve and maintain constant plasma drug concentrations.[48] It combines a loading dose with an infusion rate that decreases exponentially. The simplest case of this infusion regimen uses data from a two-compartment open pharmacokinetic model of the drug being infused. The loading dose is chosen to produce exactly the desired plasma drug concentration after mixing within the initial volume of distribution (V_C):

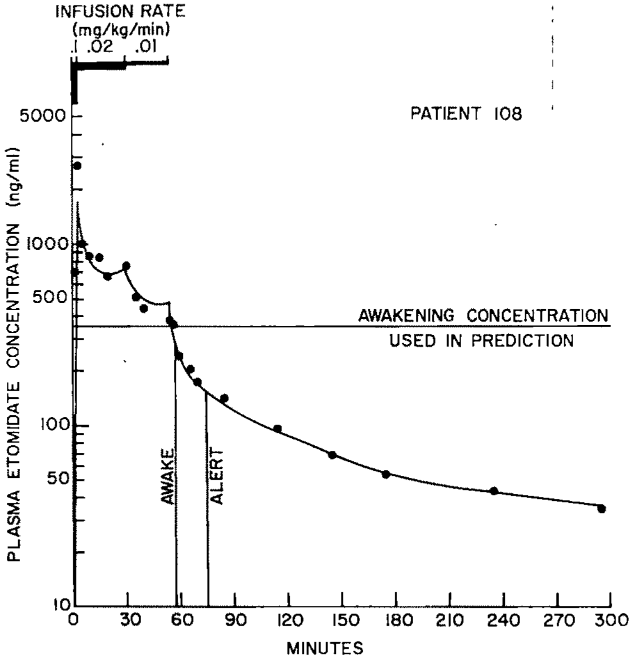

Figure 12. The plasma etomidate concentration versus time relationship during and after a three-stage infusion of etomidate with an indication of the time of awakening and alertness.[32] This infusion is based on simulations using the previously reported pharmacokinetics of etomidate.[85] (*From* Fragen RJ, Avram MJ, Henthorn TK, et al: A pharmacokinetically designed etomidate infusion regimen for hypnosis. Anesth Analg 62:654–660, 1983; with permission.)

$$\text{Dose} = C_{SS} \cdot V_C \tag{7}$$

The maintenance infusion rate decreases exponentially, with the exponential decrease in drug distribution, until, at the end of drug distribution, the infusion is the clearance matched maintenance infusion (equation 6):

$$I = C_{SS}\,(CL_E + CL_I e^{-k_{21}t}) \tag{8}$$

where CL_I is intercompartmental clearance, k_{21} is the rate constant from the peripheral compartment to V_C, and t is time. This approach to infusions has seldom been used because of the practical difficulty of easily producing an exponentially decreasing infusion rate in the clinical setting. Recent developments now make the use of such infusions by the anesthesiologist relatively practicable.

Riddell et al described a relatively simple method of doing a Krüger-Thiemer infusion that uses readily available equipment and supplies.[64] The exponentially decreasing drug infusion rate they described is produced by infusing a dilute drug solution at a constant rate (equation 6) into a mixing chamber containing a concentrated drug solution; the concentration of drug in the mixing chamber de-

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creases exponentially as the contents of the mixing chamber are infused at a constant rate into the patient. This infusion technique was used with reasonable success to infuse methohexital for hyponosis as a part of a methohexital N_2O/fentanyl anesthetic regimen (Fig. 13).[57] Ambre et al recently described an apparatus for administering an exponentially decreasing infusion that is as easy to set up and usé as a standard intravenous system (Fig. 14).[1]

Another way to administer drugs on the basis of their pharmacokinetics is by computer-controlled infusion pumps. These pumps can be programmed, on the basis of the pharmacokinetic model, to provide, on command, plasma drug concentrations adequate for the various levels of surgical stimulation. Some of the computer-controlled infusion pump algorithms based on approximations of the pharmacokinetic differential equations have inherent errors that make it impossible for them to accurately respond to a command to vary plasma drug concentrations.[78] A new algorithm uses Euler's numerical method to solve the pharmacokinetic differential equations and adjusts the rate of infusion every 5 to 15 seconds.[78] A comparison of the Euler algorithm with earlier software in a laboratory simulation has demonstrated its superiority; such a computer-controlled infusion pump has the potential of being for intravenous anesthetics what the vaporizer has been for volatile anesthetics.[78]

The preceding infusion regimens are based either on average

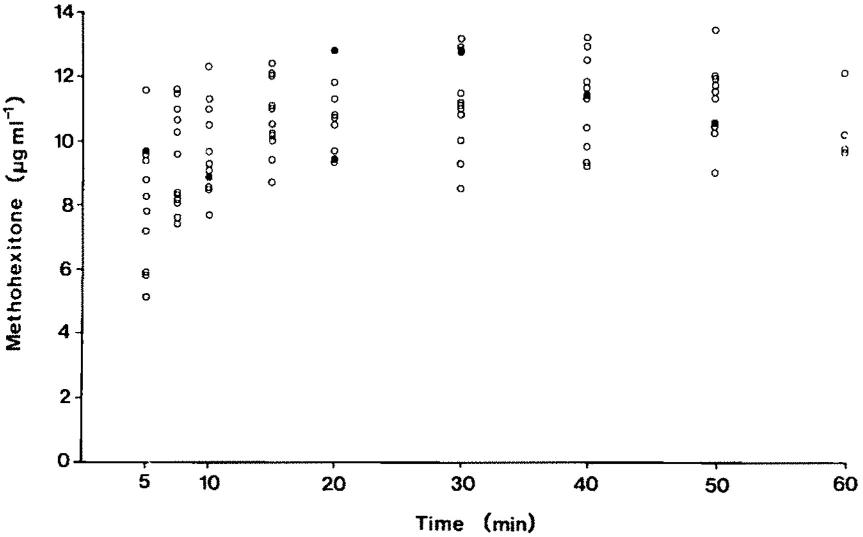

Figure 13. The plasma methohexital concentration versus time relationships for 12 patients during an infusion of the drug[57] using the exponential decreasing infusion method of Krüger-Thiemer.[48] The solid circles represent coincident points. (*From* McMurray TJ, Robinson FP, Dundee JW, et al: A method for producing constant plasma concentrations of drugs: Application to methohexitone. Br J Anaesth 58:1085–1090, 1986; with permission.)

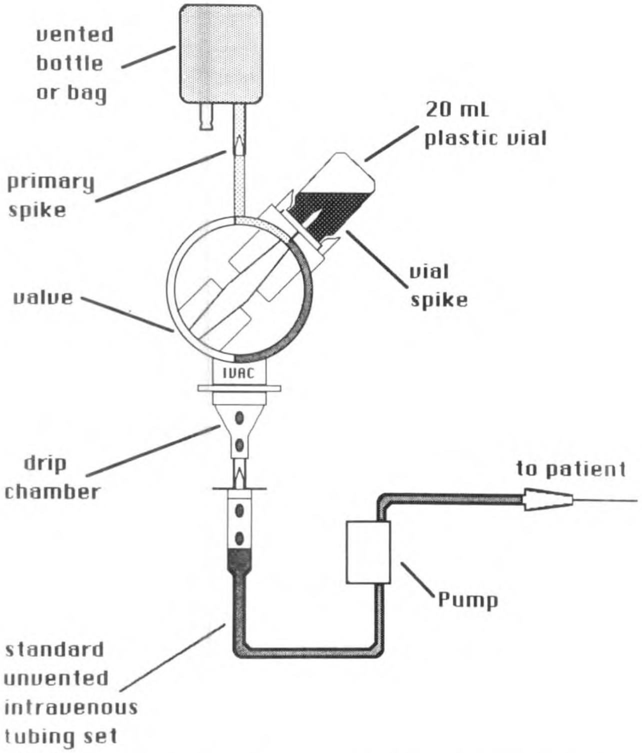

Figure 14. An illustration of the apparatus for administering an exponentially decreasing infusion of drug as described by Ambre and colleagues.[1] This apparatus is reported to be as easily set up and used as a standard intravenous system. (This is a previously unpublished figure and is reproduced with the kind permission of John J. Ambre, MD, PhD.)

pharmacokinetic data from single, relatively small studies or on population kinetic data from very large or muliple studies and on average effective plasma drug concentrations. They are open-loop systems and, as such, make no formal allowance for individualizing an infusion to a patient. Instead, the effective plasma concentration may be conservatively chosen (for example, as the average concentration plus 1 SD) so the infusion based on average kinetic variables will produce and maintain effective concentrations in nearly all patients. This means the plasma drug concentrations achieved in some patients may be relatively high and recovery may be prolonged, especially for drugs with low CL_E. Such prolongation of recovery may be expected because the longer an infusion lasts, the less recovery depends on drug distribution and the more it depends on CL_E.[60] An alternate approach to an open-loop infusion regimen is to choose as the target plasma concentration the average effective concentration, in which case one runs the risk of producing less than effective plasma concentrations in some patients by an infusion based on average or population pharmacokinetic variables.

One way to avoid the potential problems associated with open-loop infusion regimens is to use a closed-loop infusion regimen. A closed-loop infusion is based on average or population pharmacokinetic variables and average effective plasma drug concentrations, as are the open-loop infusions described previously, but is individualized to a patient by feedback control of the infusion rate, which closes the loop. Such a regimen requires an unequivocal measure of drug effect to provide the initial endpoint measurement and to monitor the endpoint that the infusion must rapidly achieve and maintain. A computer monitoring the measured effect adjusts the rate at which the infusion is being given, increasing it if the effect is too low, decreasing it if the effect is too great, and maintaining it if the effect is appropriate. This type of infusion necessarily requires expensive and complex equipment.

Feedback control has been applied to infusions of muscle relaxants for which there is an unequivocal measure of effect, the electromyogram.[25] A diagram of the control system used to infuse vecuronium in this manner is presented in Figure 15. The closed-loop infusion of vecuronium was demonstrated to be superior to manual administration because it required less drug per unit time and produced less deviation in the EMG from the setpoint.[25] It did, however, take longer to produce the initial endpoint with the closed-loop technique.

Methohexital was also infused by a closed-loop system, using an EEG endpoint of 2 to 3 Hz, in volunteers receiving either no stimulus or random tactile or audible stimuli.[73] This infusion succeeded in maintaining the endpoint in the stimulated volunteers (Fig. 16) but failed to do so in the unstimulated volunteer. In addition, the time to awakening after discontinuing the infusion was prolonged (median 21 minutes). These problems may be due to either the inappropriate choice of the EEG endpoint or the basic pharmacologic properties of

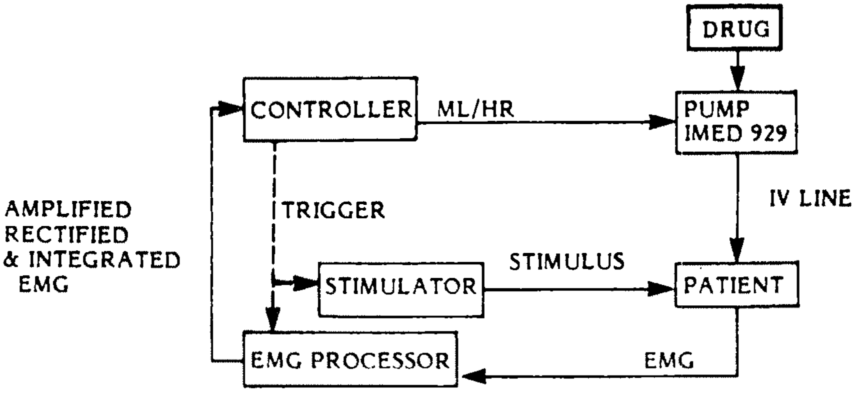

Figure 15. A diagram of the control system for the closed-loop infusion of muscle relaxants described by Ebert et al.[25] EMG = electromyogram. (*From* Ebert J, Carroll SK, Bradley EL, Jr: Closed-loop feedback control of muscle relaxation with vecuronium in surgical patients. Anesth Analg 65:S44, 1986; with permission.)

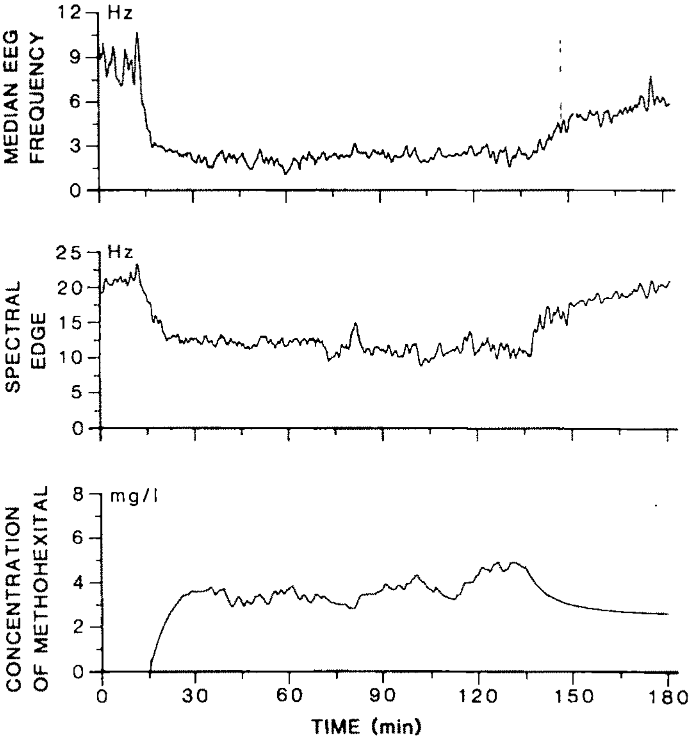

Figure 16. Predicted plasma methohexital concentration versus time relationship and corresponding measured spectral edges and median EEG frequencies during a closed-loop infusion of the drug in a randomly stimulated volunteer.[73] The infusion was controlled by the median EEG frequency. (*From* Schwilden H, Schüttler J, Stoeckel H: Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. Anesthesiology 67:341–347, 1987; with permission.)

the intermediate CL_E methylated barbiturate being infused. Nonetheless, it clearly demonstrates that given an appropriately chosen hypnotic and measure of effect, closed-loop infusions of such drugs are possible and may in fact represent the future of anesthesia.

A closed-loop infusion system without an unequivocal measure of effect is the variable rate alfentanil infusion advocated by Ausems et al[5] and Shafer et al.[77] Such an infusion relies on the anesthesiologist to monitor the clinical signs of anesthetic depth and adjust the infusion accordingly, just as they would adjust the concentration of a volatile anesthetic on the basis of the patient's needs. The new Bard Alfentanil Infusor (Fig. 17) should make it possible for any anesthesiologist to administer alfentanil in such a manner. After inserting a 60 ml syringe containing undiluted alfentanil, the anesthesiologist provides the patient's body weight and the selected loading dose and initial infusion rate. The anesthesiologist then activates the pump by selecting the bolus mode then the infusion mode and may easily adjust the infusion rate or provide an additional bolus dose (within ex-

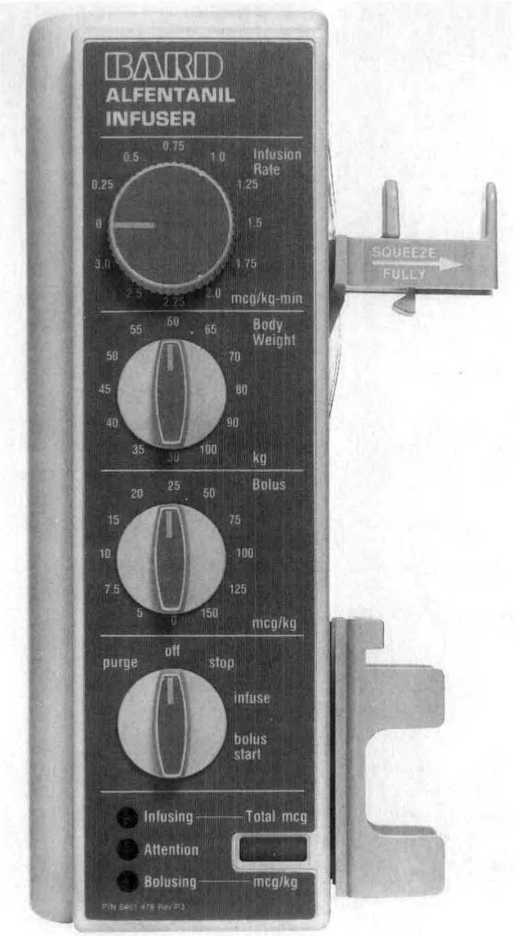

Figure 17. A photograph of the BARD Alfentanil Infuser, which is designed to conveniently and accurately infuse alfentanil according to the anticipated or observed needs of the patient. (Bard Med Systems Division, C. R. Bard, Inc., Murray Hill, New Jersey, 07974; reproduced with permission.)

pected clinical limits) at any time based on the clinical signs of anesthetic depth. While such an infusion pump is currently available only for alfentanil, it will provide the anesthesiologist unfamiliar with infusions with a friendly introduction to their possibilities.

SUMMARY

The optimum administration of drugs during the course of an anesthetic requires a precise knowledge of pharmacokinetics and pharmacodynamics. Some recent work has demonstrated that clearer and more accurate information about these relations can be obtained with greater facility with the use of the latest advances in clinical pharmacology study design and data analysis. The influences of age, anesthetic drugs, and genetics may account for some of the important interindividual variability in kinetics and dynamics. Delineation of the qualitative and quantitative influence of these and other factors should improve clinical anesthetic care. This may occur by the avoidance of dose-related side effects and the application of creative and new methods of administering already existant drugs (for example, exponentially tapering drug infusions). Much of what is new in anesthetic drugs is intimately tied to the principles of pharmacokinetics and pharmacodynamics. Therefore, anesthesiologists should be conversant with the terminology and concepts used by investigators in this field so that new information can be assessed and, if appropriate, incorporated into anesthesia practice.

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What's New in Inhaled Anesthetics?

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INHALED ANESTHETICS AND MYOCARDIAL OXYGEN BALANCE: EXPERIMENTAL MODELS AND CLINICAL STUDIES

The coronary circulation consists of large proximal coronary arteries that branch to form an intramyocardial network of small arteries and arterioles. The proximal arteries are large-bore epicardial vessels that contribute little to the total vascular resistance of the coronary system. They are the site of fixed arteriosclerotic lesions and dynamic obstruction (spasm). Nitroglycerin dilates these large arteries. The coronary arterioles are located in the myocardium and provide the major vascular resistance of the coronary system. The arteriolar response to adenosine and other metabolic products modulates a tight coupling of oxygen supply and demand. Drugs that dilate arterioles have the potential to create a diversion ("steal") of collateral blood supply from ischemic areas to non-ischemic areas. Adenosine and dipyridamole are examples of such arteriolar dilators.

Animal Studies

The occurrence of a coronary steal may be limited to very specific conditions. In a dog model, dipyridamole does not cause a decrease in collateral perfusion in the presence of a single ligated coronary artery if there is no flow restriction in the other coronary arteries. A steal only occurs in the presence of a stenosis of the coronary artery that supplies collateral flow to the ischemic area. Arteriolar dilation causes a decrease in perfusion pressure distal to the stenosis. Thus a *decrease in collateral perfusion pressure* seems to be the mechanism for the decrease in the collateral flow observed with coronary arteriolar vasodilators[6] (Fig. 1). A reduction in collateral flow may also occur in the presence of a single coronary lesion if perfusion pressure or total coronary flow are sufficiently reduced.[6,10,21]

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Isoflurane was shown to be an arteriolar vasodilator in the intact dog. No significant increase in coronary flow was observed following the administration of 0.75 per cent isoflurane. However, a significant dose-dependent increase in coronary flow was seen following the administration of 1.5 per cent and 2.25 per cent isoflurane. High-resolution coronary angiography demonstrated no dilation of coronary arteries. Thus, coronary arterioles were the site of dilation. This study utilized a fentanyl-pentobarbital control. A range of coronary perfusion pressures and myocardial oxygen consumption levels was compared.[66] Less sensitive experimental designs or species differences can account for the failure of other studies to demonstrate arteriolar dilation.[35,48]

It was also shown in a dog model that isoflurane-induced arteriolar dilation can cause a decrease in collateral coronary blood flow. An experimental preparation provided control of heart rate, blood pressure, and coronary perfusion. The effects of halothane, isoflurane, and adenosine were compared in a model of chronic coronary constriction. Isoflurane and adenosine decreased the ratio of collateral:normal flow. Halothane had no effect on coronary flow.

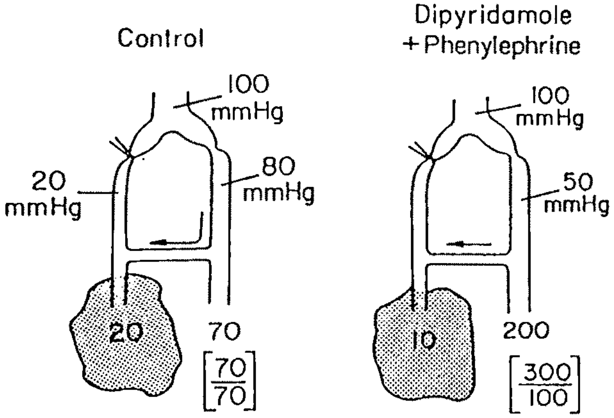

Figure 1. Schematic diagram of coronary circulation showing proposed mechanism for dipyridamole-induced coronary steal. Coronary artery divides into two branches, one completely occluded, the other stenosed but providing collaterals to the first. *Left,* distal pressure is low in the arterial bed and there is a small gradient in mean pressure across the stenosis. Flow in the ischemic region (*dotted area*) is 20 ml/min/100 gm and is determined by the collateral driving pressure, or the difference between distal pressures in the bed supplying collaterals (80 mm Hg) and the ischemic bed (20 mm Hg). Flow in the distribution of the stenotic vessel is normal at 70 ml/min/100 gm and is evenly distributed between subendocardium (*lower value in bracket*) and subepicardium (*upper value*). *Right,* during dipyridamole, with blood pressure maintained constant by phenylephrine, flow increases in the nonischemic bed to 200 ml/min/100 gm but becomes maldistributed between subendocardium and subepicardium. In addition, pressure distal to the stenosis falls to 50 mm Hg, causing a reduction in collateral driving pressure. As a result, flow to the ischemic region decreases to 10 ml/min/100 gm, interpreted as a coronary steal. (*From* Becker LC: Conditions for vasodilator induced coronary steal in experimental myocardial ischemia. Circulation 57:1108, 1978; with permission.)

However, it should be noted that a decrease in collateral flow with isoflurane could only be demonstrated when the coronary flow was decreased to the point at which contractile dysfunction occurred. This was the point at which vasodilator reserve was exhausted, and represented a 26 per cent reduction in coronary flow. No significant change in collateral flow occurred with the administration of isoflurane if coronary flow was not restricted.[10]

This contrasts with a swine model of coronary stenosis, in which a greater reserve of coronary dilation and improved survival were noted with isoflurane when compared with halothane.[17,60] This may reflect a species difference. Alternatively, no steal occurs in the presence of only a single coronary lesion.[6] If coronary steal occurs it may not be the primary determinant of survival. Similarly, halothane reversed prostanoid-induced constriction of porcine coronary artery segments. Isoflurane had no such effect.[8] This, too, may reflect a species difference. Prostanoid induced *arterial* constriction may have little bearing on the factors affecting *arteriolar* constriction.

Enflurane was not investigated in the above studies. However, enflurane was shown to be a coronary vasodilator in a canine model but a less potent one than isoflurane.[75] When coronary perfusion pressure (estimated by diastolic arterial pressure minus pulmonary artery occlusion pressure) reached 50 mm Hg in the presence of 1 MAC enflurane, myocardial tissue oxygen tension was significantly reduced.[17]

Summary. In summary, halothane lacks significant effects on the coronary vasculature in canine models. Enflurane possesses some coronary vasodilator effects and will cause decreased oxygenation when perfusion pressure is reduced. Isoflurane is a coronary arteriolar vasodilator in dogs. It has the potential to decrease coronary collateral flow when conditions leading to a decrease in collateral perfusion pressure occur. This may not occur in swine.

Clinical Studies

Most clinical studies assessing the effects of volatile anesthetics on the coronary circulation utilize sinus catheterization with a thermodilution catheter. The coronary sinus receives blood from 96 per cent of the veins from the left ventricular free wall and septum. Coronary blood flow, coronary sinus oxygen content, and coronary sinus lactate may be measured. Under normal aerobic conditions, a healthy heart consumes lactate, converting it to pyruvate. This lactate metabolism is expressed as a percentage extraction related to arterial lactate concentration. When oxygen supply decreases, myocardial metabolism undergoes a transition from lactate uptake to lactate production. The coronary sinus catheter yields global metabolic information. The correlation with electrocardiographic evidence of localized ischemia may range from excellent[59] to non-existent,[30] depending on the clinical circumstances.

Coronary sinus data will clearly reflect the effects of anesthetics on the coronary circulation–oxygen supply. Less obvious is the fact that alterations in the efficiency of myocardial metabolism occur with anesthetic administration—thus altering oxygen demand. This was demonstrated in a right heart bypass model in swine. Heart rate and workloads were controlled and the efficiency of myocardial metabolism was assessed. The relation of oxygen consumption to work performed varied with different anesthetics and workloads[61] (Tables 1 and 2).

Halothane. Coronary autoregulation is preserved during halothane anesthesia as demonstrated in patients with preserved[27,46,47] and impaired[59] ventricular function. A mean arterial pressure above 70 mm Hg was maintained at almost all times in these studies and heart rate was well controlled. Halothane and oxygen anesthesia preserved lactate extraction in all patients prior to surgical stimulation. However, occasional lactate production was observed with surgical stimulation.[46]

Improved hemodynamic stability and more consistent preservation of lactate extraction were demonstrated when halothane was added to 30 μg per kg of fentanyl.[43]

Enflurane. Two studies demonstrated consistent preservation of myocardial lactate extraction and hemodynamic stability with enflurane anesthesia in patients with coronary artery disease.[28,40] No evidence of coronary vasodilation was seen. In these studies, patients were premedicated and maintained on beta-blockers. Enflurane was titrated to decrease blood pressure approximately 30 per cent with induction and maintain blood pressure below control levels during coronary artery surgery.

This contrasts sharply with a study in which patients received one MAC enflurane for 30 minutes in an unstimulated state.[63] Mean heart rate was 80 beats per minute and mean coronary perfusion pressure was 40 mm Hg. Coronary vascular resistance fell, indicating a coronary vasodilator effect. Four of eleven patients became ischemic, and a maldistribution of coronary blood flow was demonstrated.

Table 1. *Myocardial Oxygen Utilization Efficiency (Per Cent)**

	WORKLOAD LEVELS (%)		
GROUP	*Low*	*Medium*	*High*
Halothane (N = 9)	11.07 ± 0.62	13.50 ± 1.19	10.98 ± 1.40
Enflurane (N = 6)	10.21 ± 0.86	11.40 ± 0.71	11.38 ± 1.27
Isoflurane (N = 5)	7.71 ± 0.64	9.93 ± 1.15	11.31 ± 1.55
Fentanyl (N = 11)	7.76 ± 0.57	10.44 ± 0.79	9.88 ± 1.10
Fentanyl + propranolol (N = 6)	9.81 ± 0.56	12.28 ± 1.00	15.38 ± 0.41

*Myocardial oxygen consumption and utilization efficiency determined in swine right-heart bypass model. (*From* Roberts SL, Tinker JH: Narcotics vs. inhalation anesthetics: Effects on regional myocardial ischemia. *In* Estafanous F (ed): Opioids in Anesthesia. Stoneham, Butterworths, 1984, p 192; with permission.)

Table 2. *Myocardial Oxygen Consumption (cc O_2/100 gm Ventricular Weight/min)**

GROUP	WORKLOAD LEVELS (%)		
	Low	*Medium*	*High*
Halothane	8.73 ± 0.65	8.79 ± 0.67	13.99 ± 2.11
Enflurane	9.07 ± 0.68	10.69 ± 1.05	16.03 ± 1.84
Isoflurane	9.71 ± 0.72	10.28 ± 0.74	13.85 ± 1.65
Fentanyl	12.70 ± 0.90	12.89 ± 0.97	18.04 ± 1.85
Fentanyl + propranolol	13.82 ± 0.87	9.49 ± 0.28	10.73 ± 0.33

*Myocardial oxygen consumption and utilization efficiency determined in swine right-heart bypass model. (*From* Roberts SL, Tinker JH: Narcotics vs. inhalation anesthetics: Effects on regional myocardial ischemia. *In* Estafanous F (ed): Opioids in Anesthesia. Stoneham, Butterworths, 1984, p 192; with permission.)

Isoflurane. Two studies involved the administration of approximately one MAC isoflurane for one-half hour in the unstimulated state to patients with coronary artery disease. Although one study involved the administration of premedication and beta blockers[27] and the other did not,[59] the results are esentially identical. The mean heart rate was over 80 beats per minute, and the coronary perfusion pressure was often under 50 mm Hg. A decrease in coronary vascular resistance indicated coronary vasodilation. Almost half of the patients in each study developed myocardial lactate production. These results are similar to those that result from the administration of enflurane in this fashion. Thus, the administration of one MAC isoflurane or enflurane for one-half hour in the unstimulated state will result in a significant incidence of myocardial ischemia. Because coronary perfusion pressure is decreased and control of heart rate is not optimal, it is difficult to evaluate the clinical significance of coronary vasodilation in this setting.

Anesthesia induced with isoflurane 0.5 per cent (end tidal)/nitrous oxide 50 per cent/oxygen was associated with only a moderate decrease in blood presure; no electrocardiographic evidence of ischemia was seen in 14 patients with coronary disease.[76] The threshold heart rate for pacing-induced ischemia was higher during isoflurane/nitrous oxide/oxygen anesthesia than in awake patients. This should not be viewed as a specific effect of isoflurane; the change in blood pressure and the anesthetic state are the probable causes of this beneficial effect.

Two studies involve the administration of isoflurane during coronary artery bypass surgery. Patients were premediated and maintained on beta-blockers. Isoflurane was administered to achieve a moderate decrease of blood pressure for induction and titrated to maintain blood pressure below control levels throughout surgery. One study involved the administration of oxygen/isoflurane.[40] Three of ten patients had myocardial lactate production prior to bypass. The peak incidence of ischemia was associated with hemodynamically unstable induction with oxygen/thiopental/isoflurane. The second study involved the administration of oxygen/nitrous oxide/isoflurane.[28] Induction was uneventful, but three of ten patients had myocardial lactate production during sternotomy. A decrease in coronary vascular resistance (indicating coronary vasodilation) only occurred during the pre bypass period *when mean arterial pressure was below control level.* In both of these studies, comparison was made with patients anesthetized with enflurane who had no evidence of myocardial lactate production despite comparable intraoperative hemodynamics.

In the study involving oxygen/isoflurane anesthesia, two of ten patients anesthetized with isoflurane had myocardial lactate production post bypass. This occurred during a period of decreased coronary vascular resistance. However, coronary vascular resistance was equally decreased 24 hours postoperatively.[40] Although no lactate production was observed post bypass in ten patients anesthetized with enflurane,[41] two of ten patients anesthetized with fentanyl/enflurane had lactate production post bypass.[42] The above studies vary greatly in the coronary vascular resistance seen 24 hours postoperatively. Thus, in these studies, coronary hemodynamics and lactate production post pump fail to fit a regular pattern and are difficult to attribute to the effects of anesthetics.

Isoflurane and Opioids. Enflurane and halothane appear to be more suitable for use as a sole anesthetic agent than isoflurane in patients with coronary artery disease. Differences in hemodynamic stability and probable coronary vasodilation may account for these findings. However, few clinicians would employ isoflurane as a sole anesthetic agent. Its use with opioids may be associated with different findings for several reasons. First, the combination of drugs will produce greater hemodynamic stability. Second, the coronary vasodilator properties of isoflurane are dose dependent.[66] When used with opioids, a lower dose of isoflurane will be required. Last, the occurrence of coronary steal is related to collateral perfusion pressure.[6] When used with opioids, the use of isoflurane may be limited to periods when perfusion pressure is at or above normal levels. As noted, coronary vasodilation has only been observed at blood pressure levels below those of control.

Four studies have assessed the use of isoflurane/opioid anesthesia during coronary artery bypass surgery. In two studies, isoflurane was administered to treat hypertension. In the other two studies, continuous administration of isoflurane maintained a moderate decrease in blood pressure.

Seven patients maintained on calcium-channel or beta-blocker drugs were anesthetized from coronary artery surgery with 30 μg per kg of sufentanil. Isoflurane was administered to treat elevations of blood pressure of 20 per cent over control (control was approximately 70 mm Hg). Two patients had evidence of ischemia during this elevation of blood pressure; this reverted when blood pressure was controlled with isoflurane. Electrocardiographic and coronary sinus data showed no evidence of ischemia with the administration of isoflurane. It should be noted that mean heart rate remained below 55 beats per minute throughout this study.[55] Similarly, 10 patients undergoing coronary artery bypass surgery were anesthetized with fentanyl/nitrous oxide/oxygen.[20] Isoflurane was administered when mean arterial pressure reached 110 mm Hg. The administration of isoflurane resulted in the reversion of ischemia in two patients; no patients became ischemic during isoflurane administration.

Continuous administration of isoflurane with opioids was assessed in a study of 27 patients with poor ventricular function.[69] Patients were randomized to receive either fentanyl, 100 μg per kg alone, or fentanyl, 15 μg per kg with isoflurane, for coronary artery bypass surgery. Blood pressure was moderately decreased from baseline in both groups. This required increased nitroglycerin administration in the fentanyl group. Transesophageal echocardiography revealed two patients with new wall motion abnormalities in each group.

In a similar study, 16 patients received 30 μg per kg of fentanyl followed by the continuous administration of isoflurane.[44] Although 2 of 16 patients had myocardial lactate production in the pre-bypass period, this did not differ from the control period. As in previous studies, decreases in the coronary vascular resistance in the pre-bypass period were associated with significant decreases in mean arterial pressure. Although 53 per cent of patients had myocardial lactate production immediately post bypass, lactate production was present in 33 per cent of patients 24 hours postoperatively. Thus, factors other than isoflurane contributed to this post bypass lactate production.

Nitrous Oxide. The effects of the addition of nitrous oxide to isoflurane,[57] halothane,[47] or enflurane have been studied during prolonged administration in the unstimulated state. These studies showed both significant myocardial depression and a tendency towards myocardial lactate production. These results contrast with those seen in patients with the stimulation of coronary artery surgery. Nitrous oxide with halothane[22] and enflurane[28] was associated with consistent preservation of myocardial lactate extraction. The addition of nitrous oxide to narcotics is associated with myocardial depression without change in myocardial lactate extraction in patients with coronary artery disease.[45] However, alterations, in regional wall motion were seen in a canine model. The addition of nitrous oxide to fentanyl-pentobarbital anesthesia was also shown to constrict epicardial arteries in a canine model.[80]

Summary. In summary:

1. Coronary perfusion pressure (estimated by diastolic arterial pressure minus pulmonary artery occlusion pressure) should be maintained above 50 mm Hg in patients with coronary artery disease. This may have particular importance during the administration of enflurane and isoflurane.
2. Halothane and enflurane may be more suitable than isoflurane for use as a sole anesthetic in patients with coronary artery disease.
3. When isoflurane is used with opioids, appropriate hemody-

namic stability with control of heart rate can be achieved. If isoflurane administration is limited to conditions in which perfusion pressure is at control levels, there is little risk of compromising myocardial oxygenation.

4. The addition of nitrous oxide to volatile anesthetics or opioids results in myocardial depression. The effects on myocardial oxygenation are variable.

INHALED ANESTHETICS AND NEUROANESTHESIA

Isoflurane and Cerebral Protection

An early attempt to assess the protective effects of anesthetics involved placing rodents in a hypoxic environment. Increased survival times relative to controls were noted with the administration of halothane, barbiturates,[64] and isoflurane.[50] However, survival times in this model may reflect anesthetic effects other than cerebral protection. Other models are more relevant to clinical settings in which the anesthesiologist may wish to provide cerebral protection. Middle cerebral artery ligation in primates is such a model. Barbiturates improved neurologic outcome in this model. This contrasts with halothane, which may worsen outcome.[39,67]

Recently, the effect of isoflurane, nitrous-narcotic, and barbiturate anesthesia were compared in primates with middle cerebral artery ligation.[49,54] Neurologic outcome was best in the barbiturate group, intermediate in the nitrous-narcotic group, and worst in the isoflurane group. It was noted, however, that significant differences in blood pressure between the groups may have influenced outcome.

The effects of isoflurane on global cerebral metabolic rate and electric activity are similar to those of barbiturates.[38] However, barbiturates depress the cerebral metabolic rate in all cerebral structures whereas isoflurane has few effects on various limbic structures and the substantia nigra.[32,54] This may be a factor in the failure of isoflurane to provide cerebral protection; there is no protection to these structures. However, different effect of barbiturates and isoflurane on cerebral vasculature, free radicals, cell membranes, or other factors may account for differences.

The critical regional cerebral blood flow is that level below which EEG signs of ischemia occur. This is 8 to 10 ml per 100 gm per minute during isoflurane/nitrous oxide/oxygen anesthesia in patients undergoing carotid endarterectomy.[36] The authors compare this value with that of 18 to 20 ml per 100 gm per minute determined during halothane/nitrous oxide/anesthesia. This decrease in the critical regional cerebral blood flow may result from a beneficial metabolic effect of isoflurane and may represent a form of cerebral protection. Pre-occlusion regional cerebral blood flow was approximately 30 ml per 100 gm per minute with isoflurane in contrast to more than 50 ml per 100 gm per minute with halothane.[68] Thus, the decrease in critical regional cerebral blood flow may reflect a difference in effects on blood flow rather than metabolic effects. However, a protective effect of isoflurane was suggested by a retrospective study of patients undergoing carotid endarterectomy. Fewer EEG changes were seen with isoflurane than with enflurane or halothane.[37]

The decrease in cortical metabolic rate seen with isoflurane may have a favorable effect on critical regional cerebral blood flow. However, in a primate model of focal ischemia, no favorable effects on neurologic outcome were seen.

Isoflurane and Controlled Hypotension

In studies with dogs, controlled hypotension to a mean arterial pressure (MAP) of 40 mm Hg induced with halothane, nitroprusside, or trimethaphan results in gross alterations in cerebral energy stores. However, controlled hypotension to the same level induced with isoflurane is associated with normal cerebral energy stores.[52] Although all agents caused similar decreases in cerebral blood flow (CBF), isoflurane was unique in causing a marked (~40 per cent) decrease in the cerebral metabolic rate (CMR).

The effects of controlled hypotension induced with isoflurane were assessed in two clinical studies of patients undergoing cerebral aneurysm clipping. In one study, hypotension was induced with oxygen/isoflurane. Nitrous oxide 10 per cent was added to the inspired gas for study purposes.[53] The cerebral metabolic rate for oxygen ($CMRO_2$) decreased 25 per cent and cerebral blood flow was unchanged. This suggests a favorable influence on the global supply and demand balance of oxygen. These results differ from those seen when oxygen/isoflurane/nitrous oxide 70 per cent was used to induce hypotension.[62] No significant change was observed in the cerebral metabolic rate for oxygen. There was a 16 per cent decline in cerebral blood flow. Although this suggests a deleterious effect on cerebral oxygen balance, cerebral venous pO_2 and lactate levels remained unchanged. No untoward clinical effects could be attributed to the anesthetic in either study.

The differences in the results of these two studies may be due to the use of nitrous oxide 70 per cent in the second study. Multiple studies have shown that nitrous oxide may increase the cerebral metabolic rate for oxygen. This may explain the lack of change in cerebral metabolic rate for oxygen in the second study. The different results for cerebral blood flow may be due to the lower mean arterial pressure in the second study (44 vs. 51 mm Hg) or to the difference in anesthetics.

In summary, two studies suggested that isoflurane-induced hypotension does not significantly disturb cerebral oxygen balance.

Intracranial Pressure

The intraoperative management of the patient with decreased intracranial compliance is a common problem facing the anesthesiologist. Intravenous agents (e.g., etomidate, barbiturates, benzodiazepines, opioids, droperidol) exert salutory effects on intracranial pressure (ICP). However, the use of these agents in adequate dosages to provide general anesthesia may result in prolonged emergence. The use of inhaled anesthetics, although allowing for prompt emergence, may be associated with increases in intracranial pressure. Comparison of the effects of the potent volatile anesthetics on cortical blood flow in humans,[15] brain protrusion in cats,[13] and cerebrospinal fluid mechanics in dogs[4,3] has shown isoflurane to be less deleterious than halothane or enflurane.

In a recent study,[31] patients undergoing craniotomy for small cerebral tumors were anesthetized with oxygen/nitrous oxide/isoflurane. Cerebral blood flow and cerebral metabolic rate for oxygen were assessed at 0.75 per cent and 1.5 per cent isoflurane. The increase in isoflurane concentration was associated with a 21 per cent decrease in cerebral metabolic rate for oxygen and no change in cerebral blood flow. Although this study demonstrates maintenance of global oxygen balance, it does not directly address the affects of isoflurane on intracranial pressure. The increase in isoflurane concentration was not associated with a change in mean cerebral blood flow; it was probably related to the 15 mm Hg decrease in mean arterial pressure in the presence of impaired autoregulation. In addition, although the mean cerebral blood flow did not change, the authors did not note whether any individual patients experienced increases in cerebral blood flow. These results are different from those of two recent studies in which the use of isoflurane concentrations greater than 1.0 per cent was associated with a decrease in cerebral perfusion pressure to below 50 mm Hg. The higher concentrations of isoflurane were associated with both a decrease in mean arterial pressure and an increase in intracranial pressure.[7,34]

Several studies assessed the effects of isoflurane/nitrous oxide anesthesia on intracranial pressure in patients undergoing craniotomy. In the earliest study,[1] lumbar cerebrospinal fluid pressure was measured prior to induction and during oxygen/nitrous oxide/isoflurane 1.0 per cent anesthesia. Although intracranial pressure rose during anesthesia with normocarbic ventilation, intracranial pressure decreased below control values with hyperventilation in all 15 patients. Similar results were seen with a recent study in which ventricular pressure was monitored during isoflurane anesthesia.[7] A decrease in pCO_2 below control levels was necessary to prevent intracranial pressure rises from isoflurane even in patients who were hypocarbic in the control period.

In another study of patients underoing craniotomy,[18] general anesthesia was induced with thiopental/lidocaine/pancuronium. During maintenance of anesthesia with 70 per cent nitrous oxide/oxygen and hyperventilation of the lungs, a subarachnoid bolt was inserted and intracranial pressure measured. Isoflurane 1.1 per cent inspired was added to the inspired gases when the scalp incision was made, and intracranial pressure was measured again at an unspecified interval. In 6 out of 14 patients, intracranial pressure rose significantly after isoflurane administration. The presence of a midline shift on the preoperative CT scan was identified as a significant risk factor for this increase in intracranial pressure. However, it was noted[16] that the changing levels of isoflurane and surgical stimulation make the interpretation of this study somewhat difficult.

Fentanyl-droperidol[34] and fentanyl-diazepam[11] prevented the rise in intracranial pressure seen with isoflurane, even in patients with elevated intracranial pressure. The addition of low-dose opioid infusions improved cerebral relaxation during O_2/nitrous oxide/isoflurane anesthesia.[9]

Studies of cerebral blood flow and cerebral metabolic rate in the rat[32] and baboon[77] suggested that at low concentrations (~0.5 MAC) of isoflurane there may be some maintenance of the flow-metabolic couple and cerebrovascular reactivity. However, clinical studies have not assessed the effects of this concentration of isoflurane on patients with intracranial pathology.

Nitrous Oxide. There are no clinical studies directly comparing the effects of nitrous oxide on cerebral blood flow and metabolic rate with the volatile agents. However, some clinicians selectively administer nitrous oxide to the exlusion of the volatile agents in patients with decreased intracranial compliance. In a recent study on dogs in which an epidural balloon was used to elevate intracranial pressure, the administration of nitrous oxide was associated with a loss of the cerebral vascular response to hypocarbia.[2] This contrasts with a clinical study in which hyperventilation of the lungs following the induction of anesthesia (presumably with barbiturates) counteracted the effects of nitrous oxide on intracranial pressure.[19] Recently, the addition of nitrous oxide to midazolam resulted in the stimulation of cerebral metabolism.[24] Studies such as these led to a recent editorial stressing the need to consider intravenous agents as alternatives to nitrous oxide.[5]

VOLATILE ANESTHETICS AND THE LIVER

In 1983, Lewis and co-workers[29] reviewed 58 cases of hepatic injury in patients exposed to enflurane. These authors postulated that enflurane might cause hepatic injury that would have clinical features similar to those seen with halothane. These clinical features included fever as a presenting symptom, jaundice occurring 3 to 21 days after exposure, and centrilobular necrosis on liver biopsy. The time course of the hepatic injury was of particular diagnostic importance. The hepatic injury that results from hypoxia typically occurs almost immediately after surgery with striking elevations of transaminases but only rarely with jaundice. Viral hepatitis acquired in the perioperative period would have an incubation period of greater than 4 weeks. In 24 cases, the clinical presentation of the patient was similar to that of halothane hepatotoxicity and the authors concluded that enflurane was the cause of the hepatic injury. This conclusion was made even though at least one third of these patients had other factors (e.g., congestive heart failure, hypoxia, biliary pathology, transfusions) that are well known to cause hepatic injury. Although enflurane can cause hepatic injury, the authors note the rarity of its occurrence. Anquest estimates that approximately 43 million anesthetics were given with enflurane by 1982. No more than 40 reported cases meet the diagnostic criteria suggested by these authors.

The assumption that enflurance might be a hepatotoxin is based on an analogy with halothane. Both are halogenated hydrocarbon anesthetics. However, hepatic injury following halothane is related to reductive metabolism, unique impairment of hepatocyte oxygenation, and/or an immune reaction involving anti-hepatocyte antibodies. These factors are not associated with enflurane.

Eger and associates[14] recently reviewed 58 cases of hepatic injury in patients exposed to enflurane. Forty-three patients were assigned to an "unlikely" group indicating the presence of other factors known to cause hepatic injury even if the clinical presentation was similar to that of halothane hepatotoxicity. Fifteen patients were assigned to a "possible" group, indicating the absence of other factors known to cause hepatic injury. The two groups were evaluated for the presence of 12 clinical variables suggestive of hepatic injury similar to that cause by halothane: prior anesthesia with a halogenated anesthetic, fever as a presenting sign, chills, nausea, anorexia, rash, eosinophilia, jaundice, bilirubin greater than 2.5 mg per dl, SGOT greater than 370 IU, centilobular necrosis on biopsy, and death of the patient. The presence of these variables did not differ between the "unlikely" and the "possible" groups. These authors concluded that the data did not demonstrate a causal relationship between enflurane and subsequent liver injury.

Stoelting et al[70] examined 45 cases of hepatic dysfunction following anesthesia with isoflurane. Using the same methodology as Eger and colleagues, they concluded that current evidence does not indicate a reasonable likelihood of an association between the use of isoflurane and the occurrence of postoperative hepatic dysfunction.

Two studies in rats pretreated with phenobarbital and subjected to hypoxia examined the effects of anesthetics on the liver. In one study,[65] microscopic evaluation of hepatic injury revealed no differences between the volatile agents, thiopental, or fentanyl. In a more recent study,[33] hepatic oxygen balance was impaired by all anesthetics. However, isoflurane affected hepatic oxygen balance the least, and no difference was seen between thiopental and enflurane. These studies suggest that any anesthetic may contribute to perioperative hepatic dysfunction. Thus, it is difficult to attribute hepatic injury specifically to a volatile agent when other anesthetics have also been used. In addition, it would seem that the substitution of other anesthetic techniques would be unlikely to change the incidence of hepatic injury.

SEVOFLURANE

Sevoflurane is an experimental potent volatile anesthetic. It is fluoromethyl-1,1,1,3,3,3 hexafluoro-2 propylether. The low blood:gas partition coefficient of 0.686[72] is a highly attractive feature of this agent, contributing to rapid induction and emergence from general anesthesia. MAC is 1.7 per cent.[26] At 1.1 MAC, sevoflurane produced almost the same degree of respiratory depression as halothane.[12] The cardiovascular depression seen with sevoflurane seems to be similar to that seen with other volatile agents. The myocardium is not sensitized to catecholamines.[78]

The potential for toxicity has been the subject of much research. In healthy human volunteers, one hour of exposure to 2.0 to 3.0 per cent sevoflurane resulted in arterial serum inorganic fluoride concentrations averaging 22 μmoles per liter.[25] This is the same inorganic fluoride concentration that is seen following 2.7 MAC hours of enflurane anesthesia. Sevoflurane undergoes significant degradation in the presence of soda lime. Potentially toxic products are an olefin, formaldehyde, hydrofluoric acid, and methanol. However, it appears that these potentially toxic products may be retained by soda lime and/or may break down to non-toxic compounds.[71,78] Studies in rats with hepatic microsomal induction exposed to sevoflurane passed through soda lime with 100 per cent, 14 per cent, and 12 per cent oxygen revealed no difference in hepatic and pulmonary injury when compared with isoflurane.[73] An earlier study suggested that administration of sevoflurane to rats in the presence of soda lime might injure the liver and kidney. However, injury was probably related to hyperthermia and a thermoregulatory defect.[23]

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What's New in Intravenous Anesthetics?

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In the 50 years since intravenous anesthetics were first introduced, induction of anesthesia by the intravenous (IV) route has become a widely accepted practice. The use of IV induction agents has increased in popularity because of the availability of safer and more efficacious drugs, rising concern over environmental pollution during induction of anesthesia with volatile agents, and patient preference for IV rather than mask inductions. Although thiopental (Penthothal) was first introduced over 50 years ago, it has proven so useful that it remains the "standard" induction agent against which all of the more recently introduced drugs must be compared.

What physical and pharmacologic properties would an ideal IV induction drug possess? First, the drug should be water-soluble, nonirritating, stable in aqueous solutions, and possess a long shelf-life. Second, it should produce a rapid (one arm-to-brain circulation time) and smooth onset of hypnotic action without cardiorespiratory depression. Third, it should possess both analgesic and amnestic properties. Finally, recovery of consciousness should be rapid and smooth as a result of redistribution of the drug (from the vessel-rich tissues to lean muscle and fat) and biotransformation to inactive metabolites.

Although the ideal IV anesthetic is not currently available, the comparative pharmacokinetic profiles and pharmacodynamic effects of the IV anesthetic agents that are currently used in anesthesia will be reviewed. In addition to the barbiturate compounds, drugs with a wide variety of pharmacologic properties will be discussed, including imidazoles, benzodiazepines, arylcyclohex-ylamines, and alkylphenols (Fig. 1). The clinical pharmacology and uses of the newer IV induction agents (namely, etomidate, midazolam, S(+) ketamine, and propofol) will be compared with the widely used barbiturate compounds.

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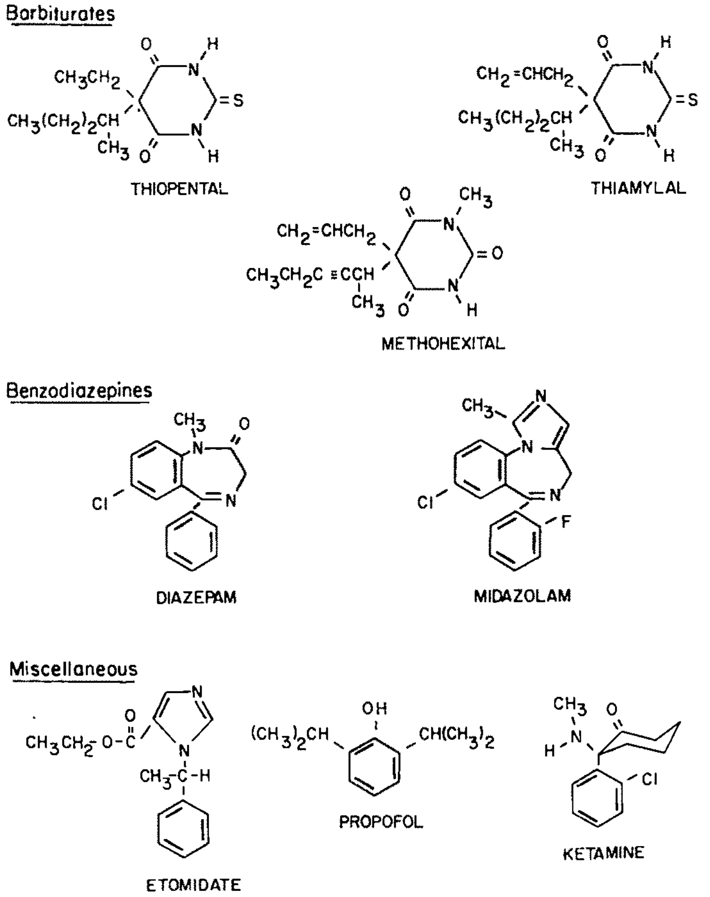

Figure 1. Chemical structures of the intravenous anesthetics that are used for the induction of anesthesia. (*From* Fragen RJ, Avram MJ: Comparative Pharmacology of Drugs Used for the Induction of Anesthesia. Chicago, Year Book Medical, 1986; with permission.)

BARBITURATES

The three commonly used barbiturate compounds are thiopental (Pentothal), methohexital (Brevital), and thiamylal (Surital). The barbiturates are rapid and short-acting IV anesthetic agents (Table 1). Thiamylal is only slightly more potent than thiopental, while methohexital is two to three times more potent than thiopental. All three drugs are water-soluble molecules with limited chemical stability in aqueous solutions. Following the usual induction dose of thiopental (3 to 6 mg per kg IV), loss of consciousness is seen within 30 seconds because of its high lipid solubility and pKa of 7.6 (60 per cent unionized at physiologic pH). Methohexital is slightly less lipid soluble and less ionized at physiologic pH than the prototypic compound. A typical 2.5 per cent solution of thiopental is alkaline (pH > 10) and thus can be irritating if it is inadvertently injected extravenously. Even

Table 1. *Induction Characteristics of the Available IV Induction Agents*

DRUG GROUP	DRUG NAME	DOSE (mg per kg)	ONSET (sec)	DURATION (min)
Barbiturates	Thiopental	3.0–6.0	<30	5–10
	Thiamylal	3.0–5.0	<30	5–10
	Methohexital	1.0–2.0	<30	5–10
Imidazoles	Etomidate	0.2–0.4	15–45	5–10
Benzodiazepines	Diazepam	0.3–0.6	45–60	15–30
	Lorazepam	0.03–0.06	60–120	60–120
	Midazolam	0.2–0.4	30–60	15–30
Arylcylohexylamines	Ketamine	1.0–2.0	45–60	10–20
Alkylphenols	Propofol	1.5–3.0	15–45	5–10

Adapted from Fragen and Avram, 1986.

though barbiturate solutions are extremely alkaline, injection of the usual concentrations (for example, thiopental 2.5 per cent or methohexital 1 per cent) result in a low incidence of postoperative venous irritation.

The barbiturates produce dose-dependent depression of central nervous system (CNS) function, resulting in a spectrum of effects ranging from sedation through coma. Increasing doses of thiopental will produce progressive slowing of the electroencephalogram (EEG; Fig. 2). The induction dose-response relationship for the barbiturate compounds is affected by many factors, including age, ASA physical status, preoperative anxiety level, and adjunctive drugs (for example, opioid analgesics, ketamine). The decreased thiopental dosage requirement in the elderly appears to be related to a decrease in the

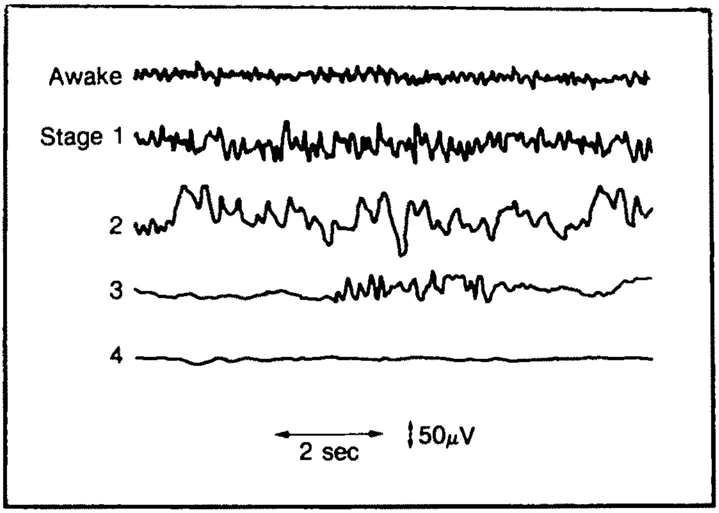

Figure 2. Changes in EEG pattern with increasing concentrations of thiopental. Loss of consciousness (hypnosis) occurs early during stage 1. (*From* Hudson, et al: A model for studying depth of anesthesia and acute tolerance to thiopental. Anesthesiology 59:301–308, 1983; with permission.)

drug's initial distribution volume (that is, a pharmacokinetic change) rather than an increase in the brain's sensitivity to thiopental (that is, a pharmacodynamic change). In contrast to thiopental and thiamylal, methohexital may be associated with pain on injection as well as excitatory activity during induction (for example, myoclonus, hiccoughing; Table 2). Recovery of consciousness occurs 5 to 10 minutes after an induction dose of thiopental (or methohexital) as a result of rapid redistribution from the brain to lean muscle and fatty tissues.

Both thiopental and methohexital have short distribution and redistribution half-life values (Table 3). However, the clearance rate for methohexital is three to four times more rapid than thiopental, resulting in an elimination half-life of 3 to 5 hours for methohexital compared with 10 to 12 hours for thiopental. Thus, full recovery from the central depressant effects of methohexital may be significantly more rapid than from thiopental when repeated doses are administered. Nevertheless, recovery of fine motor skills will require 6 to 8 hours after an induction dose of methohexital. When used for sedation or hypnosis during minor outpatient procedures, a carefully titrated, variable-rate infusion of methohexital can provide for optimal intraoperative conditions and a more rapid emergence with minimal residual CNS impairment.

Rapid short-acting IV anesthetics like thiopental and methohexital are well-suited for continuous administration techniques. Compared with intermittent bolus injections, the use of a continuous infusion will decrease the anesthetic requirement, improve cardiorespiratory stability, provide for a more rapid recovery, and decrease side effects. Barbiturate infusions have also been used for maintenance of anesthesia as the hypnotic component of a balanced anesthetic technique (for example, neuroanesthesia), as well as for sedation during local and regional anesthesia. Although prolonged infusions of thiopental have been used for sedation of agitated ventilator-dependent patients in the intensive care unit (ICU), recovery can be prolonged

Table 2. *Relative Incidence and Severity of Side Effects During the Induction Period*

DRUG GROUP	DRUG NAME	PAIN*	EXCITATION	RESPIRATORY DEPRESSION
Barbiturates	Thiopental	0	0	+ +
	Thiamylal	0	0	+ +
	Methohexital	+ +	+ +	+ +
Imidazoles	Etomidate	+ + +	+ + +	+
Benzodiazepines	Diazepam	+ + +	0	+
	Lorazepam	+ +	0	+
	Midazolam	+	0	+
Arylcylohexylamines	Ketamine	0	+ +	0
Alkylphenols	Propofol	+ + +	+	+ +

*0 to + + + represents increasing incidence and/or severity.
Adapted from Fragen and Avram, 1986.

Table 3. *Pharmacokinetic Profiles of Drugs Used for IV Induction of General Anesthesia**

DRUG GROUP	DRUG NAME	DISTRIBUTION HALF-LIFE (min)	ELIMINATION HALF-LIFE (h)	CLEARANCE (ml · min^{-1})	VDSS† (L)
Barbiturates	Thiopental	2–4	10–12	180–200	100–200
	Thiamylal	NA	NA	NA	NA
	Methohexital	5–6	3–5	700–900	60–80
Imidazoles	Etomidate	2–4	2–5	800–1400	200–400
Benzodiazepines	Diazepam	10–15	20–40	15–35	60–100
	Lorazepam	3–10	10–20	50–70	50–90
	Midazolam	7–15	2–4	300–550	70–130
Arylcyclo-hexylamines	Ketamine	11–17	2–3	1250–1400	200–250
Alkylphenols	Propofol	2–4	1–3	1400–2800	200–500

†Vdss = volume of distribution at steady-state.

because of the slow clearance rate and long elimination half-life of thiopental (compared with the newer IV anesthetic agents).

An induction dose of a barbiturate compound will produce an anesthetic state characterized by a loss of consciousness (hypnosis) and amnesia. These sedative-hypnotic compounds are classified as antanalgesics because they appear to lower the pain threshold. As a result, painful stimuli (for example, laryngoscopy and intubation) elicit marked increases in mean arterial pressure (MAP) and heart rate (HR) (Table 4). However, the transient hemodynamic changes during the induction period are of little clinical significance in most patients. Furthermore, intracranial pressure (ICP) is decreased to a greater extent than arterial pressure following induction with thiopental and hence, cerebral perfusion pressure (CPP) is usually increased. The ability of these compounds to decrease the cerebral metabolic rate for oxygen (CMRO$_2$) while maintaining cerebral perfusion is useful in managing patients with increased ICP. In addition to their cerebral

Table 4. *Comparative Hemodynamic Effects of IV Anesthetics During Induction (1 to 2 Minutes After IV Injection) and Postintubation (1 to 2 Minutes After Laryngoscopy)*

		INDUCTION		INTUBATION	
DRUG GROUP	DRUG (DOSE RANGE*)	MAP	HR	MAP	HR
Barbiturates	Thiopental, 3–6 mg/kg	↓	↑	↑	↑
	Thiamylal, 3—5 mg/kg	↓	↑	↑	↑
	Methohexital, 1—2 mg/kg	↓	↑	↑	↑
Imidazoles	Etomidate, 0.2–0.4 mg/kg	→	→	↑	↑
Benzodiazepines	Diazepam, 0.3–0.6 mg/kg	→	→	↑	↑
	Lorazepam, 0.03–0.06 mg/kg	→	→	↑	↑
	Midazolam, 0.2–0.4 mg/kg	→	→	↑	↑
Arylcyclohexylamines	Ketamine, 1–2 mg/kg	↑	↑	↑	↑
Alkylphenols	Propofol, 1.5–3.0 mg/kg	↓	→	↑	↑

*Lower dosages are recommended when these drugs are used in combination with opioid analgesics and when administered to geriatric and critically ill patients.

protective and anticonvulsant effects, the barbiturates will also decrease intraocular pressure (IOP).

Barbiturates produce dose-related depression of both the cardiovascular and respiratory systems. The decrease in tidal volume noted during induction often progresses to apnea. The incidence of apnea is primarily related to the dose and rate of drug administration. Short-lived depression of central respiratory drive (that is, CO_2-responsiveness) has been reported following induction doses of thiopental. The transient hypotension noted during induction with thiopental results from both direct myocardial depression, which decreases stroke volume, and dilatation of the venous capacitance vessels leading to a decreased venous return to the heart. Although barbiturates can decrease central sympathetic outflow, compensatory baroreceptor-mediated reflex sympathetic stimulation produces tachycardia in response to decreases in blood pressure.

IMIDAZOLES

Etomidate (Amidate) is a carboxylated imidazole-containing compound that is structurally unrelated to any other IV anesthetic. It is a sedative-hypnotic compound characterized by a rapid onset of action and recovery, excellent cardiovascular and respiratory stability, and the absence of histamine release. Etomidate is a weak base that is dissolved in propylene glycol and therefore, its use is associated with pain and occasional venoirritation when it is rapidly infused for induction of anesthesia.

IV injection of etomidate produces a rapid loss of consciousness with minimal cardiovascular or respiratory changes. The duration of CNS depression is dose-dependent, with return of consciousness occurring 5 to 10 minutes after the usual induction dose of etomidate, 0.2 to 0.4 mg per kg IV. Recovery of psychomotor function after etomidate is intermediate between thiopental and methohexital. Redistribution of etomidate from the brain to other less-well perfused tissue compartments appears to be responsible for its relatively short duration of action. The drug is rapidly metabolized by hepatic microsomal enzymes and plasma esterases to inactive carboxylic acid metabolites. The total body clearance rate for etomidate is five times greater than thiopental's and contributes to a shorter elimination half-life (2 to 5 hours). Etomidate's pharmacokinetic variables are similar regardless of whether an intermittent bolus or continuous infusion technique is used for administering the drug (Table 5).

The EEG changes produced by etomidate are similar to those produced by the barbiturates and other sedative-hypnotic compounds. Like the barbiturates and benzodiazepines, etomidate possesses anticonvulsant activity. Etomidate also decreases cerebral blood flow (CBF), $CMRO_2$, and ICP without producing significant changes in CPP. The prominent myoclonic activity noted during induction of anesthesia with etomidate may result from disinhibition of

Table 5. *Comparative Effects of Bolus Versus Infusion Administration Techniques on Etomidate Pharmacokinetics*

INVESTIGATORS	INJECTION TECHNIQUES	KINETIC MODEL	ELIMINATION HALF-LIFE (min)	CLEARANCE (ml per min)	VDSS (L)
van Hamme et al (1978)	Bolus	3	210	880	260
Schüttler et al (1980)	Infusion	2	110	1700	250
Schüttler et al (1980)	Infusion	2	60	1600	140
de Ruiter et al (1981)	Infusion	3	170	1280	310
Fragen et al (1983)	Bolus	2	70	1600	160
Wagner et al (1984)	Bolus	3	280	870	340

Adapted from Swerdlow and Holley, 1987.

subcortical neuronal acitivity. Pretreatment with an opiate analgesic (for example, fentanyl 2 to 10 μg per kg) markedly attenuates the myoclonic activity, as well as the pain on injection. Since etomidate lacks analgesic properties, the use of fentanyl (or one of its newer analogs) prior to induction of anesthesia with etomidate will also blunt the hemodynamic response to laryngoscopy and intubation (Table 4).

When etomidate is used for induction of anesthesia in patients with cardiac disease, it appears to produce minimal effects on cardiovascular function. Etomidate does not significantly alter heart rate or cardiac output, although slight decreases in blood pressure might result from decreases in peripheral vascular resistance. Etomidate produces a favorable balance between myocardial oxygen supply and demand (as the increase in myocardial blood flow exceeds the increase in myocardial metabolism). Contrary to most other IV and inhaled anesthetics, etomidate does not decrease hepatic or renal perfusion. Since effects on CBF and ICP are minimal, etomidate appears to be the induction agent of choice in neurosurgical patients with increased ICP and cardiovascular disease. Respiratory depression appears to be dose-related, involving both respiratory rate and tidal volume, although the magnitude is less than that produced by equihypnotic doses of the barbiturate and benzodiazepine compounds. Etomidate also causes a decrease in IOP similar to thiopental.

The use of etomidate for induction and/or maintenance of anesthesia in the outpatient setting may be associated with a high incidence of postoperative nausea and vomiting. However, the incidence can be decreased by the prophylactic administration of an antiemetic drug (for example, droperidol 0.6 to 1.2 mg, metoclopramide 10 to 20 mg IV). Finally, etomidate produces transient postoperative suppression of adrenal steroidogenesis. This effect appears to result from enzymatic blockade of the adrenal steroidogenic pathway lasting for 6 to 8 hours after an induction dose. The clinical significance of this transient, drug-induced adrenal suppression is unknown. Prolonged infusions of etomidate are contraindicated in critically ill patients because the adrenal suppressive effects of etomidate may predispose these patients to septic complications. However, short infusions (30 to 90 minutes) can be effective adjuvants during balanced anesthesia, as well as for sedation during local or regional anesthesia.

BENZODIAZEPINES

The three parenteral benzodiazepines of interest to anesthesiologists are diazepam (Valium), lorazepam (Ativan), and midazolam (Versed). All benzodiazepines possess similar anxiolytic, sedative, hypnotic, amnestic, anticonvulsant, and muscle relaxant properties. Both diazepam and lorazepam are insoluble in water and thus the parenteral formulations contain propylene glycol. The injection of propylene glycol is associated with pain and occasionally venous irritation. Midazolam is a newer benzodiazepine that is available in a water-soluble formulation. Midazolam's parenteral solution (pH 3.5) consists of water-soluble salts that cause minimal local irritation after IV or intramuscular injection. At physiologic pH, an intramolecular rearrangement occurs that changes the physicochemical properties of midazolam such that it becomes more lipid soluble (Fig. 3). Although both diazepam and lorazepam are lipid soluble, neither drug is ideal for induction because of their slow and somewhat unpredictable onset of action. Because of the marked temporal lag between its peak blood concentration and maximal clinical effects, lorazepam is particularly difficult to titrate intravenously during the induction period. Midazolam, on the other hand, has a rapid onset of of action and can be a useful alternative to the barbiturate compounds for induction of anesthesia.

Biodispositional events such as tissue distribution and redistribution (from the vessel-rich tissues to lean muscle) are important in terminating the sedative-hypnotic properties of the benzodiazepine compounds. The low hepatic clearance rates for diazepam and

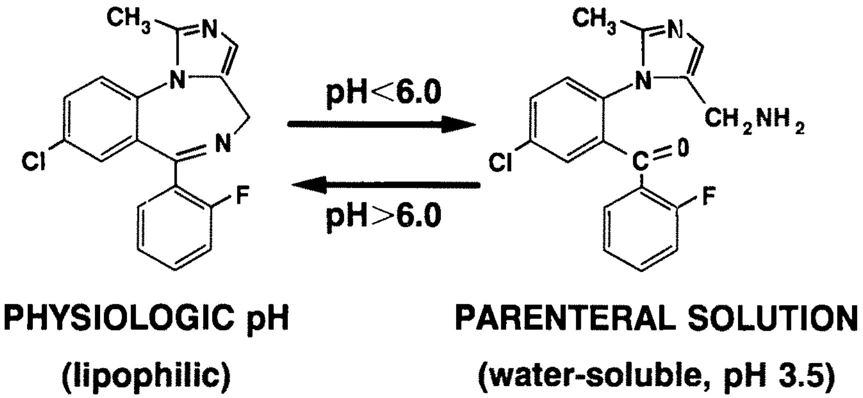

Figure 3. Effect of pH on the chemical structure of midazolam, a water-soluble benzodiazepine. (*From* White PF: Pharmacologic and clinical aspects of preoperative medication. Anesth Analg 65:963–974, 1986; with permission.)

lorazepam result in terminal elimination half-life values of 20 to 40 and 10 to 20 hours, respectively (Table 3). On the other hand, midazolam is more rapidly and extensively metabolized by the hepatic microsomal enzyme system, resulting in a shorter elimination half-life (2 to 4 hours). In contrast to diazepam, the short half-lived hydroxylated metabolites of midazolam appear to have minimal CNS activity. As a result, recovery of fine motor skills should be more rapid when repeated doses or a continuous infusion of midazolam are used for sedation during local or regional anesthesia (compared with diazepam and lorazepam). However, recent data would indicate that recovery of psychomotor and cognitive function is slower after sedation with midazolam when compared with thiopental, methohexital, and etomidate.

When midazolam was used for induction of anesthesia in outpatients undergoing short surgical procedures (<45 minutes), it was associated with a slower onset of action, a more prolonged recovery period, and a higher incidence of postoperative amnesia than thiopental or methohexital. In contrast to the barbiturates, anterograde amnesia or lack of recall is a consistent component of the CNS action of benzodiazepines. Prolonged emergence from anesthesia can occur when either midazolam or diazepam are used for induction of anesthesia. Although benzodiazepines are capable of producing loss of consciousness, they appear to have a limited efficacy as primary anesthetics. Both diazepam and midazolam produce decreases in the volatile anesthetic requirement, however, a plateau or "ceiling effect" has been reported. Thus, benzodiazepines are most effective when used as IV adjuvants for induction and maintenance of anesthesia. Midazolam can also markedly attenuate the cardiostimulatory effects of ketamine and minimize its emergence sequelae.

When used as an adjuvant to other drugs for induction of anesthesia (Table 6), benzodiazepines exhibit minimal cardiovascular depressant effects. However, use of midazolam for induction of anesthesia can cause greater decreases in blood pressure than diazepam because of its ability to decrease peripheral vascular resistance and dilate venous capacitance vessels. Nevertheless, both diazepam and midazolam are associated with stable cardiac function when used for

Table 6. *Combinations of IV Sedative: Analgesic Drugs Used for Induction of General Anesthesia*

1. Diazepam 0.2–0.4 mg/kg, and fentanyl 10–75 μg/kg
2. Midazolam 0.1–0.2 mg/kg, and ketamine 0.5–1.0 mg/kg
3. Thiopental 2–3 mg/kg, and ketamine 0.5–1.0 mg/kg
4. Fentanyl 2–10 μg/kg, and thiopental 2–3 mg/kg
5. Fentanyl 2–10 μg/kg, and etomidate 0.2–0.4 mg/kg
6. Fentanyl 2–10 μg/kg, and midazolam 0.1–0.2 mg/kg
7. Sufentanil 0.25–0.75 μg/kg, and thiopental 2–3 mg/kg
8. Sufentanil 0.25–0.75 μg/kg, and midazolam 0.1–0.2 mg/kg
9. Alfentanil 20–60 μg/kg, and thiopental 2–3 mg/kg
10. Alfentanil 20–60 μg/kg, and midazolam 0.1–0.2 mg/kg

induction of anesthesia (Fig. 4). Although benzodiazepines produce negative inotropic effects, direct myocardial depression is probably of little clinical significance. Benzodiazepines also reduce circulating catecholamine levels and decrease the workload of the heart; however, the baroreflex mechanism is unaltered.

Apnea occurs less frequently after induction with diazepam and midazolam than thiopental. Yet, rapid injection of midazolam produces dose-related respiratory depression that is similar to that produced by equipotent doses of thiopental. In patients with chronic obstructive pulmonary disease, ventilatory depression after midazolam is more prolonged than with thiopental. The respiratory depressant effects of midazolam can be minimized by using small bolus doses or a carefully titrated infusion. Midazolam, 0.15 to 0.3 mg per kg IV, produces minimal changes in ICP and CPP when used to induce patients with intracranial mass lesions and decreased intracranial compliance. Analogous to the barbiturate compounds, the dose-dependent decreases in $CMRO_2$ and CBF suggest that midazolam can protect against cerebral hypoxia.

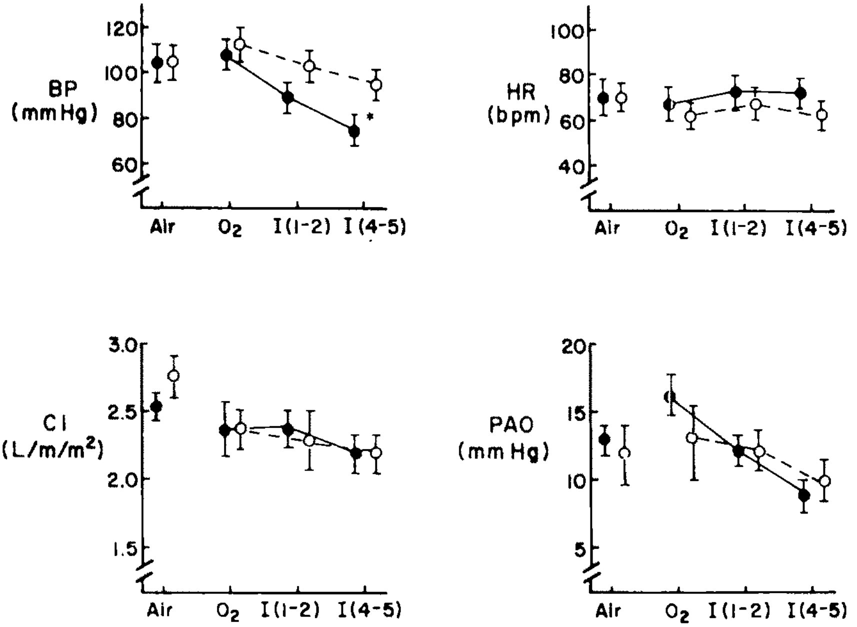

Figure 4. Hemodynamic variables in patients with ischemic heart disease induced with midazolam, 0.2 mg per kg intravenously (●———●) or diazepam, 0.5 mg per kg intravenously (○- - -○). HR = heart rate; BP = mean blood pressure; CI = cardiac index; and PAO = pulmonary artery occluded pressure. The comparisons between midazolam and diazepam were significant at $P < .05$ (*). Determinations were made while the patient was breathing room air ("Air"), breathing 100 per cent oxygen (O_2), 1 to 2 minutes following induction (I[1–2]), and 4 to 5 minutes following induction (I[4–5]). (*From* Samuelson, et al: Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. Anesth Analg 60:802–809, 1981; with permission.)

Induction of anesthesia with benzodiazepines is characterized by marked variability in the dose-response relationships (even though maximal CNS effects occur 3 to 5 minutes after IV injection of diazepam or midazolam). The use of opiate premedication and/or larger doses of these drugs (for example, midazolam 0.3 to 0.4 mg per kg IV) will decrease the variability. Males seem to be more sensitive to benzodiazepines than females. As expected, elderly, hypovolemic, and critically ill patients require lower doses for induction. Midazolam is used for induction and maintenance of anesthesia as part of a nitrous oxide-narcotic-relaxant (so-called "balanced") technique because of its prominent amnestic properties. However, recovery may be prolonged compared with the traditional combination of thiopental, volatile agent, and nitrous oxide.

Benzodiazepines remain the most widely used drugs for sedation and relief of acute anxiety (anxiolysis) during the perioperative period. It is important to remember that midazolam has a steeper dose-response curve than diazepam (Fig. 5), and therefore, careful titration is necessary to avoid complications related to oversedation. Although a specific benzodiazepine antagonist (flumazenil) will be available in the near future to reverse excessive sedation, the risk of over-sedation can be minimized by administering small bolus doses or by using a variable-rate infusion of the benzodiazepine agonist. When midazolam infusion (0.5 to 5 μg per kg per minute) is used for sedation in the ICU, it has been shown to control agitation and decrease the opioid analgesic requirement without producing cardiovascular or respiratory instability. However, marked variability exists in the individual

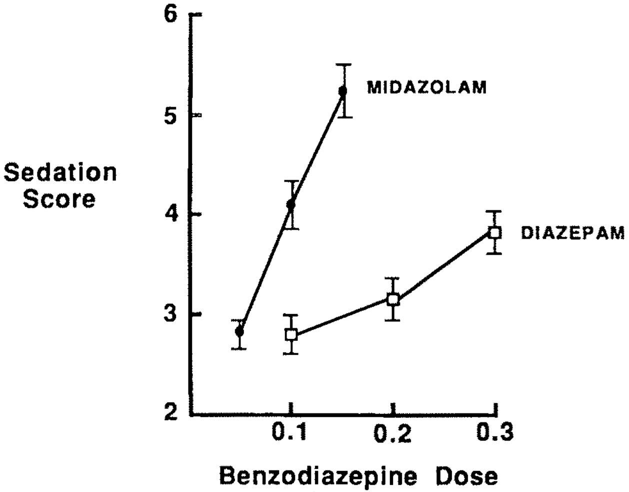

Figure 5. Relationship between the sedation score and the initial intravenous dose of midazolam or diazepam (mg per kg). Sedation scores of 2 = awake/relaxed to 6 = asleep/unarousable. (*From* White PF, et al: Comparison of midazolam and diazepam for sedation during plastic surgery. J Plast Reconstruc Surg, May, 1988; with permission.)

patient dose-effect relationships. In addition, recent data suggest that tolerance may develop to the CNS effects of midazolam.

ARYLCYCLOHEXYLAMINES

Ketamine (Ketalar, Ketaject) is a so-called "dissociative" anesthetic, which is structurally related to phencyclidine (PCP). The water-soluble ketamine molecule, has a pKa of 7.5, a lipid solubility ten times greater than thiopental, and contains a chiral center producing two optical isomers, S(+) ketamine and R(−) ketamine. Ketamine is a rapid-acting CNS depressant that produces sedation, hypnosis, amnesia, and analgesia. The clinical usefulness of the racemic mixture (containing equal amounts of the two optical isomers) has been limited because of its cardiovascular-stimulating properties and the high incidence of disturbing emergence reactions.

The S(+) ketamine isomer offers some clinical advantages over the racemic mixture because it is a more effective anesthetic and analgesic drug. Quantification of verbal responses in the postanesthetic period suggested that more agitation and psychic emergence reactions occurred after administration of R(−) ketamine than the racemic compound or S(+) ketamine. A more recent study in healthy young volunteers indicated that S(+) ketamine was three to five times more potent than the R(−) isomer in terms of its anesthetic effects. However, both isomers produced similar degrees of cardiovascular stimulation and psychomimetic activity. The pharmacokinetic variables for the individual ketamine isomers did not differ from those for the racemic mixture (Table 3). Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers revealed that R(−) ketamine was not as effective as racemic or S(+) ketamine in causing EEG slowing (Fig. 6), these data suggest that the R(−) isomer can function as a partial agonist (or an agonist-antagonist) with respect to its effects on the CNS.

Following IV administration, ketamine is rapidly distributed to highly perfused tissues and subsequently redistributed to muscle and fat in a fashion analogous to thiopental and midazolam. Ketamine is rapidly metabolized by the liver and its principal metabolite, norketamine, is pharmacologically active. The clearance of ketamine is dependent on hepatic blood flow and the elimination half-life is 2 to 3 hours (Table 3). Although the high clearance rate limits its effectiveness following oral or rectal administration ("first pass effect"), ketamine is a useful intramuscular induction agent prior to an inhalational (volatile) agent in patients without venous access.

Ketamine produces a "dissociative" anesthetic state, described as a functional and electrophysiologic dissociation between the thalamoneocortical and limbic systems. This unique clinical anesthetic state is characterized as a state of catalepsy in which the eyes remain open with a slow nystagmic gaze while corneal and light reflexes remain intact. The analgesia produced by ketamine appears related to interference with the transmission of the affective-emotional component of

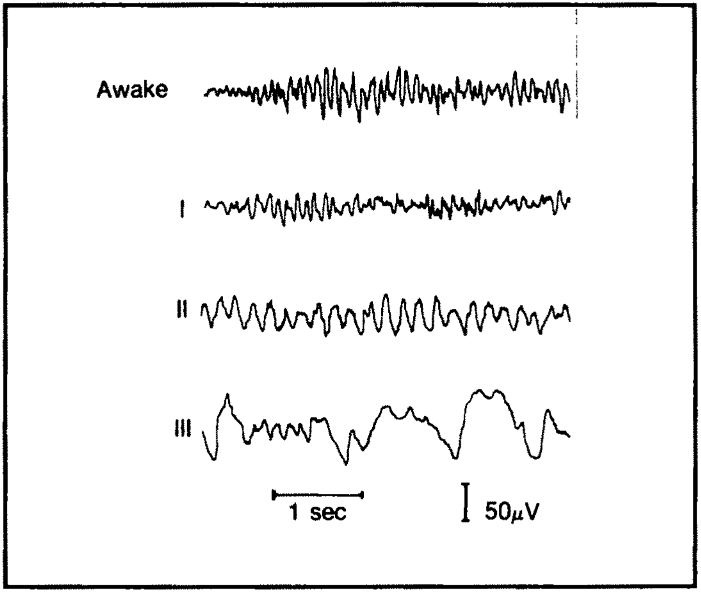

Figure 6. Progressive changes in the EEG produced by ketamine. Phases I to III are seen with racemic ketamine and its S(+) isomer. With R(−) ketamine, phase II was the maximal EEG depression produced. (*From* Schüttler, et al: Pharmacodynamic modeling of the EEG effect of ketamine and its enantiomers in man. J Pharmacokinet Biopharm 15:241–253, 1987; with permission.)

pain from the spinal cord to higher brain centers. In addition, ketamine has opioid-like activity at laminae specific spinal cord mu-receptors. Ketamine increases both cerebral blood flow (CBF) and ICP as a result of its ability to increase systemic blood pressure and to produce cerebral vasodilatation.

Coronary vasodilatation also occurs with ketamine, however, it does not appear to be sufficient to compensate for the increase in afterload and cardiac work imposed by ketamine. The cardiovascular stimulatory effects of ketamine result from peripheral vasoconstriction and an increase in heart rate secondary to direct CNS stimulation and inhibition of postganglionic reuptake of norepinephrine. If the sympathetic nervous system is blocked, ketamine has the ability to produce direct myocardial depression and peripheral vasodilatation.

In contrast to the opioid analgesics, only transient respiratory depression is seen after induction doses of ketamine (1 to 2 mg per kg IV). Lower doses of ketamine (<1 mg per kg) can stimulate the ventilatory drive as evidenced by a leftward shift in the CO_2-response curve. In patients with reactive airway disease, ketamine may be the IV agent of choice because of its ability to decrease airway resistance and reduce bronchospasm. Ketamine can relax bronchial smooth muscle and potentiate the bronchodilating effects of epinephrine. Despite alleged retention of the protective pharyngeal and laryngeal reflexes, tracheal soiling and aspiration is reported following induction of anesthesia with ketamine. Thus, one should *not* assume that the use of ketamine obviates the need for endotracheal intubation in the patient with a "full stomach."

Ketamine (0.5 to 1.0 mg per kg IV) can be an extremely valuable induction agent for patients suffering from acute hypovolemic shock. Lower doses of ketamine can also be used to produce sedation and analgesia in high-risk patients where a period of hypotension or apnea could be life-threatening. In contrast to the usual cardiostimulatory response to ketamine, critically ill patients may respond to ketamine with an unexpected drop in blood presssure as a result of the inability of the sympathomimetic actions of ketamine to counterbalance its direct myocardial depressant and vasodilatory effects.

The prominent psychomimetic activity during emergence from ketamine anesthesia has limited its use in clinical practice. However, when ketamine was used as part of a rapid-sequence induction technique prior to cesarean section, the incidence of undesirable emergence reactions was surprisingly low. Nevertheless, a high incidence of side effects is often seen when ketamine is used as the sole agent for induction of anesthesia. Several investigators have reported a decrease in side effects when ketamine was used in conjunction with either intravenous or inhaled anesthetics. The benzodiazepines (for example, midazolam) are the most effective drugs for attenuating ketamine-induced cardiovascular stimulation and emergence sequelae. If benzodiazepine premedication is contraindicated, it should be administered on emergence from ketamine anesthesia.

Pretreatment with an antisialagogue is recommended to avoid respiratory problems (for example, coughing, laryngospasm) secondary to ketamine-induced salivary gland secretions. During balanced anesthesia with midazolam (or thiopental) and nitrous oxide, use of a ketamine infusion, 25 to 50 μg per kg per minute, will improve the cardiovascular stability and decrease the total dosage requirement compared with the traditional incremental dosing method. Ketamine infusion (5 to 25 μg per kg per minute, has also been used for sedation and analgesia during local anesthesia. Recent studies indicate that ketamine infusion is also extremely effective for sedating agitated, ventilator-dependent patients in the ICU. When used in this situation, it significantly decreases the opioid analgesic requirement.

ALKYLPHENOLS

Propofol (Diprivan) is a rapid-acting IV anesthetic that is virtually insoluble in aqueous solution. This novel sedative-hypnotic compound is classified as a hindered phenol. Propofol has recently been solubilized in a lecithin-containing emulsion (10 per cent Intralipid) and is currently undergoing extensive clinical investigation in the United States. In contrast to the original "cremophor EL" formulation, the propofol emulsion has not been associated with hypersensitivity or analphylactic reactions.

Propofol has a simple molecular structure (that is, 2,6-

diisopropylphenol) and a high lipid solubility, which enhances its ability to cross the blood brain barrier. The rapid onset and recovery after a single induction dose of propofol compares favorably with methohexital and thiopental. In contrast to the barbiturates, there appears to be less residual postoperative sedation ("hangover" effect) and psychomotor impairment with propofol (Fig. 7). In addition, the incidence of postoperative side effects (for example, drowsiness, nausea, and vomiting) is extremely low. The lower incidence of nausea and vomiting with propofol (compared to the other available IV anesthetics) can contribute to earlier ambulation and discharge after outpatient surgery.

Induction of anesthesia with propofol (1.5 to 3 mg per kg IV) produces a rapid onset of anesthesia (<60 seconds) lasting 5 to 10 minutes. Decreased induction dosages are recommended for elderly and hypovolemic patients, as well as for patients premedicated with CNS depressant drugs. When lower doses of propofol, 1 to 2 mg per kg, are used for induction of anesthesia in combination with opioid

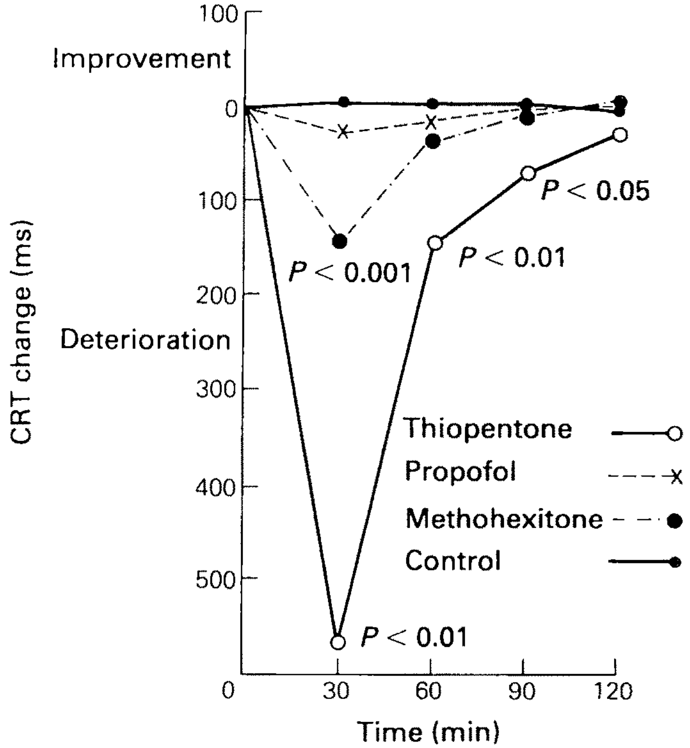

Figure 7. Comparison of mean changes in choice reaction time (CRT) during the early postoperative period in untreated controls and outpatients who received either thiopental, methohexital, or propofol for induction of anesthesia. (*From* Grant IS, MacKenzie N: Recovery following propofol (Diprivan) anaesthesia—A review of three different anaesthetic techniques. Postgrad Med J 61 (suppl 3):133–137, 1985; with permission.)

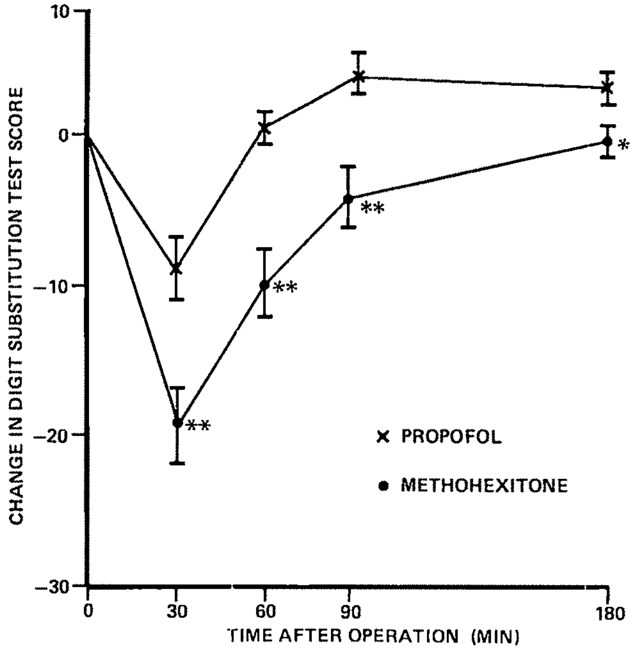

Figure 8. Recovery of cognitive function after outpatient anesthesia with alfentanil and propofol compared with alfentanil and methohexital. (*Adapted from* Kay B, et al: Intravenous anesthesia for cystoscopy: A comparison of propofol or methohexitone with alfentanil. Eur J Anaesthesiol 3:111–120, 1986; with permission.)

analgesics (for example, alfentanil 15 to 30 μg per kg) for short outpatient procedures, recovery is extremely rapid (Fig. 8). Preliminary studies indicate that the drug is rapidly redistributed and eliminated from the body (Table 3). Compared with other IV anesthetics, metabolism of propofol is extremely rapid. After only 30 minutes, less than 20 per cent of an IV bolus dose of propofol can be recovered as the unchanged compound. The total body clearance rate for propofol exceeds hepatic blood flow. While hepatic metabolism obviously plays a crucial role in the clearance of propofol, other tissues may also be involved in the rapid elimination of this drug (for example, lung). Approximately 90 per cent of the drug is excreted in the urine as water-soluble glucuronide and sulfate conjugates. There are no known active metabolites of propofol.

Propofol is an effective induction and maintenance hypnotic agent that produces dose-dependent cardiovascular and respiratory depression. At equipotent doses, propofol appears to be similar to thiopental and methohexital with respect to its cardiovascular and respiratory depressant properties. Propofol has been reported to produce greater changes in arterial blood pressure and systemic vascular resistance than thiopental, whereas changes in heart rate and cardiac stroke volume were less prominent after induction with propofol. Propofol does not impair baroreflex sensitivity; however, central sympatholytic mechanisms result in a stable heart rate despite decreases in arterial pressure. Although the incidence of apnea with propofol is comparable to the barbiturate compounds, the duration of the apneic episodes is somewhat longer. Typically, a rapid reduction in tidal volume and tachypnea precede the apneic period. Transient depression of central respiratory drive would be expected after an induction dose of propofol.

When compared with methohexital for induction and mainte-

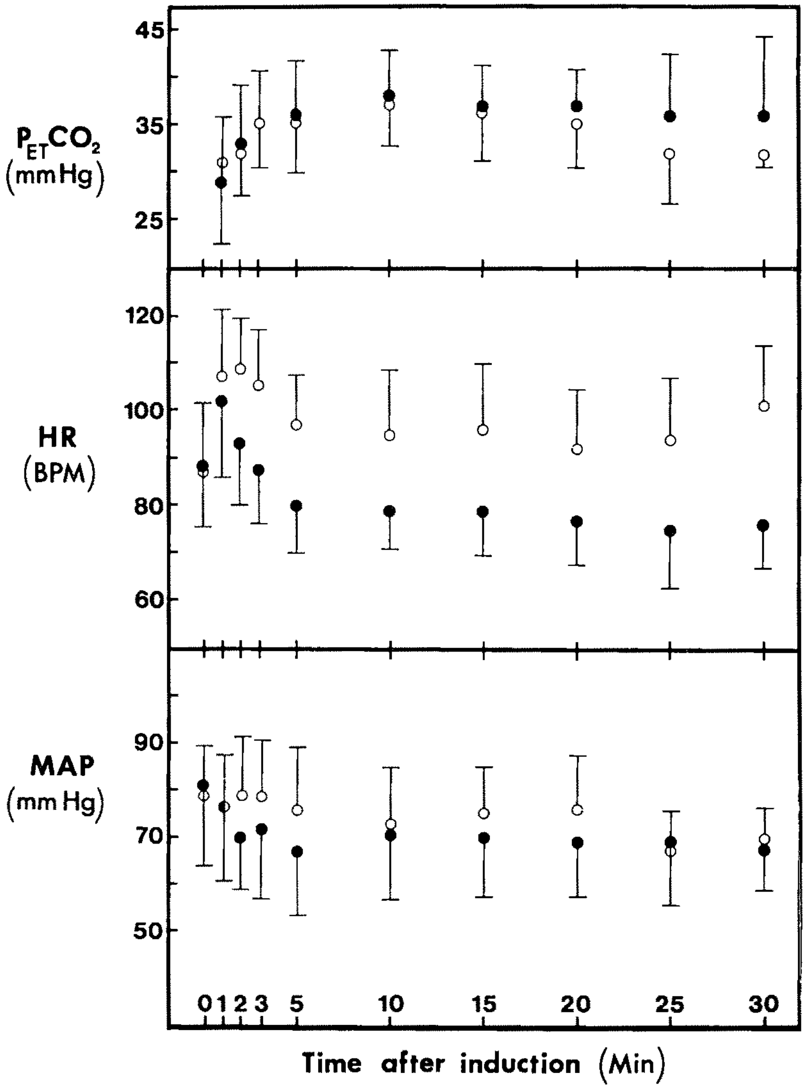

Figure 9. Cardiorespiratory effects of propofol (●) and methohexital (○) when administered with nitrous oxide during ambulatory surgery. (*From* Doze, et al: Comparison of propofol with methohexital for outpatient anesthesia. Anesth Analg 65:1189–1195, 1986; with permission.)

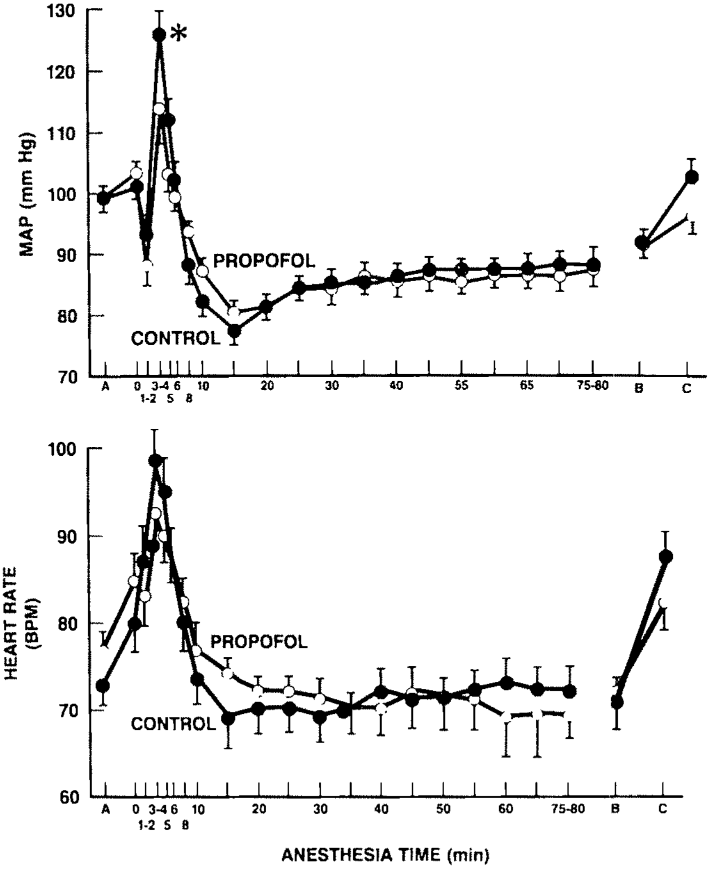

Figure 10. Comparative effects of thiopental-isoflurane-N_2O (○) and propofol-N_2O (●) on mean arterial pressure (MAP) and heart rate (HR) during superficial surgical procedures. The letters on the abscissa correspond to the following events: *A*, preinduction (3 to 5 minutes prior to the administration of meperidine, 1 mg · kg^{-1} intravenously, and d-tubocurarine, 2 to 3 mg intravenously; *B*, end of anesthesia (on the discontinuation of N_2O); and *C*, post extubation (5 minutes after removal of the endotracheal tube). An asterisk denotes significant differences ($P < .05$). (*From* Doze, et al: Comparison of propofol with thiopentalisoflurane for induction and maintenance of outpatient anesthesia. Anesthesiology 65A:544, 1986; with permission.)

nance of outpatient anesthesia, propofol appeared to possess similar cardiorespiratory properties (Fig. 9). In addition, the cardiovascular effects of propofol are comparable to the volatile anesthetics when used for maintenance of general anesthesia (Fig. 10). While propofol may not possess analgesic properties, in contrast to thiopental it does not appear to decrease the analgesic threshold. Preliminary studies suggested that propofol could enhance the neuromuscular blocking actions of the nondepolarizing muscle relaxants. Like the other IV anesthetics, propofol produces a 25 to 50 per cent decrease in IOP. Because of the low incidence of postoperative nausea and vomiting

Table 7. *Comparison of Recovery Times (minutes) After Methohexital-Nitrous Oxide (Methohexital) and Propofol-Nitrous Oxide (Propofol) for Outpatient Anesthesia*

	METHOHEXITAL	PROPOFOL
Time from end of maintenance infusion to		
Awakening	5.6 ± 3.1	5.0 ± 2.2
Response	6.0 ± 3.2	5.4 ± 2.2
Orientation	6.4 ± 3.2	5.6 ± 2.3
Time from discontinuation of N_2O to		
Awakening	2.9 ± 1.8	1.9 ± 1.3
Response	3.3 ± 1.9	2.3 ± 1.3
Orientation	3.6 ± 1.9	2.5 ± 1.4†
Ambulation	81 ± 23	67 ± 24†

*Mean ± SD.

†Significantly different from methohexital, $P < .05$.

From Doze VA, et al: Comparison of propofol with methohexital for outpatient anesthesia. Anesth Analg 65:1189–1195, 1986; with permission.

after propofol anesthesia, some investigators have suggested that propofol may actually possess antiemetic properties. Obviously, further studies are needed to substantiate these clinical observations.

When a variable-rate propofol infusion was used for maintenance of anesthesia as part of a "balanced" technique, recovery times were found to compare favorably with methohexital following outpatient anesthesia (Table 7). In addition to a more rapid emergence from anesthesia, recovery of psychomotor and cognitive skills was also more rapid after propofol-nitrous oxide anesthesia compared with a conventional technique consisting of thiopental-isoflurane-nitrous oxide (Table 8). Recent studies would also indicate that propofol compares favorably with methohexital and midazolam when used for sedation during local or regional anesthesia.

The effects of propofol on cerebral hemodynamics and metabolism have not been extensively studied. Analogous to the other sedative-hypnotic induction agents, propofol would be expected to de-

Table 8. *Comparison of Recovery Times (minutes) After Outpatient Anesthesia with Propofol-Nitrous Oxide (Propofol) or Thiopental-Isoflurane-Nitrous Oxide (Isoflurane)*

TEST	ISOFLURANE	PROPOFOL*
Awakening	7.8 ± 6.6	3.6 ± 2.9
Orientation	11.3 ± 9.2	5.8 ± 4.2
P-deletion test	110 ± 51	78 ± 37
Trieger test	141 ± 59	87 ± 44
Sedation analog scales	175 ± 63	119 ± 58

*Significantly different from control group, $P < .05$

From Doze VA, White PF: Comparison of propofol with thiopental-isoflurane for induction and maintenance of outpatient anesthesia. Anesthesiology 65A:544, 1986; with permission.

Table 9. *Effect of Injection Site on the Incidence of Pain During Induction of Anesthesia*

DRUG	DOSE (mg per kg)	INCIDENCE OF PAIN ON INJECTION (%)	
		ANTECUBITAL FOSSA	DORSUM OF HAND
Thiopental	4.0–5.0	4	5
Etomidate	0.3	14*	29*
Methohexital	1.5	18*	41*
Propofol	2.0–2.5	8	31*

*Significantly different from thiopental group, $P < .05$.

From McCollum JSC, et al: Comparison of induction characteristics of four intravenous anaesthetic agents. Anaesthesia 41:995–1000, 1986; with permission.

crease CBF, $CMRO_2$, and ICP. Although induction with propofol has been associated with muscle tremors, it appears to have anticonvulsant properties similar to the barbiturate compounds. Side effects following propofol administration include pain on injection (Table 9), and occasionally, patients will experience dizziness, involuntary muscle movements, coughing, euphoria, and postoperative headaches.

DRUG COMBINATIONS

Since none of the available IV induction agents rapidly achieve an adequate depth of anesthesia without producing significant cardiorespiratory changes or other disturbing side effects (for example, pain, myoclonus, excitatory activity), the use of drug combinations has become increasingly popular. In most clinical situations, the use of a benzodiazepine or opioid analgesic as the sole agent for induction of anesthesia will result in more prolonged induction and recovery times as well as a higher incidence of perioperative side effects compared with the barbiturate compounds. Thus, combining sedative-hypnotic and analgesic drugs possessing similar pharmacokinetic profiles is a logical approach (Table 6).

When an analgesic dose of an opiate (for example, fentanyl 1.5 to 3 μg per kg, sufentanil 0.15 to 0.3 μg per kg, or alfentanil 15 to 30 μg per kg) is used in combination with a sedative-hypnotic (for example, thiopental 2 to 3 mg per kg, etomidate 0.1 to 0.2 mg per kg, midazolam 0.1 to 0.2 mg per kg, or propofol 1 to 2 mg per kg), it can provide for improved hemodynamic stability during induction without increasing the incidence of preoperative or postoperative side effects. Similarly, combining a benzodiazepine (for example, diazepam 0.2 to 0.4 mg per kg, midazolam 0.1 to 0.2 mg per kg) with ketamine, 0.5 to 1.0 mg per kg, can provide for a rapid and smooth induction of anesthesia and prompt recovery without significant perioperative complications. Adjunctive use of lidocaine, 1 to 2 mg per kg IV, in combination with thiopental, 3 to 4 mg per kg IV, can also attenuate the cardiovascular responses to laryngoscopy and intubation without producing excessive hemodynamic instability. By utilizing minimally effective doses of two or more IV drugs, the anesthetist can achieve a rapid and smooth induction and emergence without untoward side effects.

SUMMARY

It is obvious that many of the goals desirable in an ideal IV induction agent have not been achieved with the currently available drugs. An ideal drug for induction of anesthesia would provide for a rapid and pleasant loss of consciousness, no cardiorespiratory changes, good operating conditions, and a rapid recovery without side effects. Although they are not ideal induction agents, the newer IV anesthetics possess some unique pharmacologic properties that may offer advantages over thiopental (Table 10).

Premedication with sedative-anxiolytic drugs (for example, midazolam, diazepam) can minimize preinduction anxiety and thereby, decrease the induction dosage requirements. In achieving a smooth induction of anesthesia, it is desirable to minimize myocardial oxygen demand and to maximize myocardial oxygen supply. Use of an induction technique that rapidly achieves an adequate level of anesthesia (hypnosis) and analgesia without producing hypotension or tachycardia is important in maintaining the crucial balance between oxygen supply and demand. If an adequate "depth of anesthesia" is not achieved during induction of anesthesia, larynogoscopy, and tracheal intubation will produce reflex sympathetic stimulation (that is, tachycardia, hypertension, arrhythmias), which may be extremely deleterious to the critically ill patient.

Thiopental remains the most widely used IV anesthetic even though it is unstable in solution, produces significant cardiovascular and respiratory depression, lacks analgesic properties, readily crosses the placental barrier, and is associated with a high incidence of postoperative drowsiness and sedation. Unfortunately, the other available IV anesthetic agents are also capable of producing adverse reactions

Table 10. *Summary of Comparative Pharmacologic Properties of Thiopental and the Newer IV Induction Drugs*

Properties	Thiopental	Etomidate	Midazolam	S(+)ketamine	Propofol
Solubility	Water	Propylene glycol	Water	Water	Egg lecithin
Dose	3–6 mg/kg	0.2–0.5 mg/kg	0.2–0.4 mg/kg	0.5–1.5 mg/kg	1.5–3.0 mg/kg
Onset	Rapid	Rapid	Intermediate	Rapid	Rapid
Induction	Smooth	Pain/ myoclonus	Smooth	Excitatory	Smooth/pain
Cardiovascular	Depression	Minimal	Minimal	Stimulation	Depression
Respiratory	Depression	Minimal	Depression	Minimal	Depression
Analgesia	None	None	None	Yes	None
Amnesia	Minimal	Minimal	Yes	Minimal	Minimal
Emergence	Rapid	Rapid	Intermediate	Intermediate	Rapid
Side effects	Drowsiness	Nausea/vomit	Drowsiness	Psychomimetic	Dizziness

when used for induction of anesthesia. Although the newer IV agents should prove to be extremely useful for both induction and maintenance of anesthesia, thiopental will likely remain the drug of choice for routine induction of general anesthesia.

In conclusion, the rational use of two or more rapid and relatively short-acting IV drugs possessing mutually complementary pharmacologic properties (for example, sufentanil-thiopental, alfentanil-propofol, or midazolam-ketamine) will allow the anesthetist to achieve a rapid and smooth induction, cardiovascular stability during the maintenance period, and a rapid recovery without adverse side effects. The availability of more rapid-acting and "controllable" IV anesthetics and analgesics should further enhance our ability to achieve optimal surgical conditions during general anesthesia.

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Newer Opioid Analgesics and Antagonists

*Carl Rosow, MD, PhD**

This article reviews the pharmacologic properties of three opioids recently introduced into clinical practice and a few that are still in clinical trials. For purposes of discussion, I have classified them pharmacodynamically as agonists, antagonists, and agonist-antagonist opioids.

Several of these agents (alfentanil, sufentanil, nalmefene) have direct, practical relevance for anesthesia practice. The remainder (agonist-antagonists, peptides) are included for their potential relevance and for what they contribute to our understanding of opioid analgesic action.

PURE OPIOID AGONISTS

Alfentanil

Alfentanil is a new tetrazole derivative of fentanyl that appears pharmacodynamically similar to the parent drug but that has a more rapid onset and shorter duration of action. In the initial animal studies, analgesia and respiratory depression were found to reach peak intensity in less than 2 minutes, and the effects of small doses were nearly gone within 10 to 15 minutes.

The pharmacokinetics of alfentanil are most easily understood when contrasted with those of fentanyl (Table 1). In most ways, the pharmacokinetic behavior of fentanyl and alfentanil is similar. Like fentanyl, a single bolus of alfentanil undergoes rapid redistribution, then slower elimination. Termination of alfentanil effects after small doses depends on redistribution, but when larger doses are administered the effect may be somewhat prolonged. The important differences between these two drugs arise from differences in their physical-chemical properties. Alfentanil is less fat soluble than fentanyl and undergoes less nonspecific binding to lipid and protein constituents

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Table 1. *Comparative Pharmacokinetics of Fentanyl and Alfentanil in Humans*

	FENTANYL	ALFENTANIL
T1/2 distribution (min)	13.4	11.6
T1/2 elimination (min)	220	92
Volume distribution (l/kg)	4.2	0.86
Protein bound fraction (%)	84	92
Clearance (ml/kg/min)	11.6	6.4
Lipid solubility (octanol:water)	860:1	130:1
pKa	8.4	6.5
Un-ionized fraction at pH 7.4 (%)	9	89
Hepatic extraction	0.62	0.50

of cells. The steady state volume of distribution for alfentanil is less than a quarter that of fentanyl. This means that considerably more alfentanil remains in the bloodstream and therefore, can be cleared by the liver. The hepatic clearance of alfentanil is actually slower than that of fentanyl, but the smaller volume of distribution makes the overall rate of elimination (and consequently, the elimination half-life) much faster.

Faster elimination means that alfentanil is much less likely to produce cumulative effects when it is given in repeated bolus doses. Even very large doses of this drug are unlikely to produce prolonged respiratory depression in most instances. Rapid elimination also makes the drug particularly well suited for administration by infusion.

In man, the peak effect of alfentanil occurs in only 90 to 120 seconds after intravenous administration. One would think that fentanyl, the more lipophilic drug, would have the more rapid onset of effect. As it turns out, both of these drugs are sufficiently fat soluble to enter the central nervous system with ease, but alfentanil is faster for several other reasons:

(1) Bower and Hull[5] showed that the *central* compartment for alfentanil is smaller, so the initial plasma level (prior to distribution) is higher. A larger concentration gradient therefore drives alfentanil from blood to cerebrospinal fluid (CSF).

(2) Alfentanil is unique among the opioid alkaloids in that it has an acid pKa (6.5). At a body pH of 7.4, alfentanil is 90 per cent un-ionized while fentanyl (pKa 8.4) is 90 per cent ionized. Only un-ionized, or uncharged, drug can cross biologic membranes and enter the central nervous system. So, not only does more alfentanil remain in the blood stream, but much more of it exists in a diffusible form.

(3) The volume of distribution within the brain itself also seems to be smaller for alfentanil than for fentanyl. This property was demonstrated in a study by Scott et al,[30] who examined EEG slowing produced in volunteers by infusions of either fentanyl or alfentanil. With fentanyl, there was a delay of several minutes between the rise in plasma drug concentration and the onset of the EEG effect. With

alfentanil, the onset of effect was nearly simultaneous with the rise in plasma level. The fentanyl effect persisted for 20 to 30 minutes after the drug infusion was stopped; after alfentanil, the EEG reverted to normal within a few minutes. The differences measured in this study may relate to the distribution of fentanyl and alfentanil within brain tissue itself.[12] Compared with fentanyl, alfentanil probably undergoes much less nonspecific binding in the brain. This theoretically leaves a larger amount of drug available for specific receptor binding, and occupancy of these sites occurs more rapidly. Regardless of how one explains these EEG findings, it is reasonable to predict that other brain effects like analgesia and respiratory depression will follow the same pattern.

As stated previously, alfentanil appears to be a typical opioid agonist. The analgesic effects are intense and dose-related. The analgesic potency is generally considered to be about one-tenth that of fentanyl, although the exact potency is still a matter of some debate.

Alfentanil may theoretically be used in any setting that calls for a potent opioid. Small doses can be used to control acute pain in awake individuals, although some sort of infusion will almost always be required. Suppression of the hemodynamic response to laryngoscopy and intubation occurs when doses of 30 to 40 μg per kg are combined with thiopental. Much higher doses (100 to 200 μg per kg and above) may be used alone for induction of anesthesia, but the hypnotic effect may be exceedingly brief.[33] Since alfentanil interacts with mu receptors in the dorsal horn of the spinal cord, it is effective when given by intrathecal or epidural routes.

The onset and duration of respiratory depression induced by alfentanil parallel the time course of analgesia. In most individuals 15 μg per kg (a dose typically used for outpatient surgery) will produce clinically apparent respiratory depression for less than 20 minutes.[29] There is no convincing evidence that any dose of alfentanil produces more or less respiratory depression than an equianalgesic dose of any other opiate. Respiratory depression is readily reversible with naloxone, and the effects of naloxone will normally outlast the effects of alfentanil.

Alfentanil may induce bradycardia due to stimulation of the central vagal nuclei. This effect is treatable or preventable with vagolytic agents such as atropine or pancuronium. It is quite possible that muscle relaxants with no vagolytic activity (for example, vecuronium) will allow more bradycardia to be produced by the opioid. Alfentanil, like all opioids, may produce systemic vasodilation due to a reduction of medullary sympathetic outflow. A few studies suggest that alfentanil may produce more vasodilation than fentanyl or sufentanil, especially when large doses are given rapidly. Clinically used doses of alfentanil do not appear to produce myocardial depression or histamine release.[33]

Alfentanil may produce the syndrome of muscle rigidity, and high doses do this with such predictability that the drug has proved useful for studying this effect. Benthuysen et al[3] have shown that alfentanil increases electromyographic activity in skeletal muscle throughout the body, not just in muscles of the trunk. These investigators believe that pronounced muscular activity is a likely explanation for the myoclonic movements and "seizures" sometimes reported during induction with high doses of the opioids. Opioid-induced rigidity may also produce hypertonus of the laryngeal and pharyngeal musculature, and this may be sufficient to produce partial upper airway obstruction. Rigidity during induction is usually prevented or reversed by small doses of nondepolarizing muscle relaxants (for example, 1 to 2 mg of pancuronium) or succinylcholine.

Postoperative nausea is a major problem in outpatient surgery, and the opioids are obviously one of the contributing factors. One study comparing fentanyl and alfentanil in outpatients suggested that alfentanil treatment was associated with a higher frequency of nausea.[37] In our experience, 25 to 40 per cent of adult ambulatory patients overall have postoperative nausea, and the problem does not seem to be more or less severe with alfentanil.

The clinical application of alfentanil that intrigues and perplexes many anesthesiologists is its use by continuous infusion. White et al[37] have successfully used alfentanil by both bolus and infusion techniques in outpatients. Infusion was more convenient, recovery was slightly more rapid, and the infusion group required a lower total dose of drug. In a subsequent study, this same group[32] found tremendous individual variability in both alfentanil pharmacokinetics and in the response to a given plasma level of the drug. Administration of alfentanil at fixed infusion rates resulted in inadequate anesthesia in some patients and postoperative depression in others.

Ausems et al[1] titrated alfentanil infusions to clinical responses in a group of general surgical patients and had much better results. The responses to various surgical stimuli were correlated with simultaneous measurements of plasma alfentanil. Tracheal intubation, for example, required an average of 475 ng of alfentanil per ml of plasma, while skin closure required only 150. Respiratory depression requiring treatment with naloxone had a 50 per cent probability of occurring at 223 ng per ml. The caveat here is still the large variability in the individual response. Some individuals apparently require 600 ng per ml or more of alfentanil for adequate anesthesia, while some need less than 200. The data show, however, that for each patient the change between adequate and inadequate anesthesia occurs over a very small range of concentrations. The challenge for the anesthesiologist is to find the *clinical* endpoint that establishes this narrow range for the individual patient.

The procedure for giving an infusion has now been made considerably easier by the availability of a small microprocessor driven syringe pump specifically designed for alfentanil. The drug may now be used without drop counting, burrettes, diluents, or tedious calculations.

Sufentanil

Sufentanil is a potent thienyl derivative of fentanyl that has been clinically available for several years. It is marketed only for intraoperative use, especially as an analgesic anesthetic for major surgical procedures.

Sufentanil is a pure opioid agonist like fentanyl, but it binds to mu receptors with almost 30 times more affinity.[35] In animals, sufentanil is roughly ten times as potent an analgesic and respiratory depressant as fentanyl; its activity appears to be comparably high in humans, although this has never been formally tested. All of sufentanil's acute effects are readily reversible by naloxone. The drug produces tolerance and physical dependence in animals and is therefore handled as a controlled substance.

Sufentanil is approximately twice as fat soluble as fentanyl, and it is distributed rapidly and extensively to all body tissues. Like all fentanyl analogues, it is cleared by hepatic biotransformation, and its metabolites account for little or none of its biologic activity. The hepatic extraction ratio is an extremely high 0.72 (that is, 72 per cent of hepatic blood flow is cleared of drug in one pass), so the total elimination of this drug is highly dependent on splanchnic blood flow. The steady state volume of distribution is 2.48 L per kg, a value midway between those for fentanyl and alfentanil. At low doses sufentanil appears to be short acting since termination of its effects depends on rapid redistribution; at higher doses, the drug appears long acting since significant plasma levels persist during the longer elimination phase.

Most of the clinical literature on this drug deals with its use in very high doses (10 to 30 μg per kg) to produce both hypnosis and analgesia for major surgery. It is not clear whether the greater potency and specificity of sufentanil constitute real advantages over fentanyl in this setting. The cardiovascular effects of sufentanil are very similar to those of fentanyl.[27,31] There is no release of histamine at any clinically relevant dose.[27] Both drugs produce moderate vasodilation and vagally mediated bradycardia. One animal study[23] suggests that sufentanil may produce a small direct vasodilator effect.

After high doses of sufentanil, the hemodynamic and hormonal responses to surgery are greatly attenuated, although some responses may still occur.[6,31] A number of clinical investigations have indicated that sufentanil may be more effective than fentanyl in suppressing hemodynamic responses during cardiovascular surgery. Recent work from our institution shows that pure opioid anesthesia (fentanyl *or* sufentanil) is frequently insufficient to block all hypertensive responses to surgery, even when doses well above the recommended range are administered.[25]

Sufentanil has been used in lower doses for conventional balanced anesthesia, but there is little to distinguish it from fentanyl in this setting. Rapid administration of sufentanil may produce the syndrome of muscular rigidity (compare alfentanil), and myoclonic movements have been described during induction with high doses of this agent. Although it is eliminated more rapidly than fentanyl, high doses of sufentanil are still capable of producing prolonged respiratory depression, so facilities for postoperative ventilation must be available.

There are only a few papers describing the use of sufentanil in settings other than balanced anesthesia. Little has been written about the use of sufentanil as an analgesic in awake patients, but there is no reason to doubt that it could be used safely and efficaciously. Of course, the formulation currently used (50 μg per ml) is inappropriate for this indication, since each milliliter of solution is equivalent to nearly 50 mg of morphine. The combination of high lipid solubility and high affinity for opioid receptors makes sufentanil an attractive choice for epidural use. Relatively high doses of sufentanil have been given by this route, and the analgesia produced was highly segmental and rapid in onset.

PURE ANTAGONISTS

The only pure antagonist currently used in anesthesia is naloxone, the N-allyl derivative of oxymorphone. Small doses of naloxone reliably reverse or prevent the effects of morphine-like or nalorphine-like opioids. Given alone, however, naloxone is virtually devoid of clinically demonstrable effects, even in doses much greater than those used for opioid reversal. Naloxone does possess some agonist effects in animals, so its classification as a "pure" antagonist may be misleading.

Clinically, naloxone is usually administered in one of two ways: it may be given in very large doses (0.8 to 2.0 mg) for the treatment of known or suspected narcotic overdose, or it may be titrated in small incremental doses (0.1 mg or less) to reverse narcotic-induced respiratory depression in the postoperative period. In the latter instance, naloxone will antagonize analgesia as effectively as it does respiratory depression, so we normally attempt to produce *partial* reversal of both.

Reversal of opioid effects does carry a small risk: Naloxone has been reported to produce vomiting, emergence delirium, arrhythmias, and even pulmonary edema in postoperative patients. Several of these case reports are difficult to explain, since some of the patients involved were young and presumably healthy, and in most cases, the naloxone doses used were very small. This intense sympathetic activation can be particularly deleterious if naloxone is used to reverse the extremely high doses of fentanyl or sufentanil commonly used in cardiovascular surgery.

Some recent papers[22] have suggested that reversal with an opioid agonist-antagonist (for example, nalbuphine) may be safer than with naloxone. Antagonists with some intrinsic analgesic properties, it is reasoned, will produce a more gradual reversal and avoid a sympathetic response. To my knowledge, there have been no convincing data to support such a view, and there are at least two good reasons not to use agonist-antagonist type drugs for reversal: (1) Nausea and arrhythmias have been described after nalbuphine reversal. (2) A mixed agonist-antagonist may either increase or decrease the opioid effect, depending on the dose administered and the amount of drug to be reversed. This principle was recently reiterated in the anesthesia literature.[2]

Naltrexone

Naltrexone is a relatively pure antagonist, which is also derived from oxymorphone. It has a longer duration of action than naloxone and somewhat greater potency. Unlike naloxone, it does not undergo extensive first-pass metabolism and is therefore effective when given orally.[36] A parenteral preparation of naltrexone is not available, but the drug has been approved for oral use in the treatment of opioid addiction. Detoxified addicts are maintained on enormous doses of naltrexone (50 mg or more), which will block most or all of the effects of injected heroin or other illicit opioids.[20] These patients are few in number, but they may represent real management problems should they require treatment for acute pain.

Nalmefene

The greatest clinical drawback to naloxone is its very brief duration of antagonist action (usually less than 1 hour). Since almost all opioid agonists have longer durations than naloxone, the antagonist must be given in repeated doses (or by infusion) to prevent renarcotization. The need for a longer acting antagonist has been evident for some time.

Nalmefene is a potent, extremely long-acting antagonist that is currently undergoing clinical trials. Gal et al[11] have shown that 1 to 4 mg of this drug will prevent the respiratory effects of repeated injections of fentanyl for up to 8 hours. It is difficult to imagine a common perioperative setting in which more than one dose of this agent would be required. Careful titration will be required, however, since exuberant use of nalmefene could eliminate effective analgesia for many hours.

AGONIST-ANTAGONISTS

This group of drugs has been developed in an effort to create a potent analgesic with reduced addiction liability. In the United States, no agonist-antagonist has attained a secure place in anesthesia practice, although several are widely used for postoperative analgesia. We now know that these opioids are a heterogeneous group that differ in some significant ways from the pure agonists. These differences may or may not be advantageous in anesthesia, but they are invaluable in furthering our knowledge of opioid action, pain, and addiction.

Nalorphine (N-allylnormorphine, the prototype agonist-antagonist) was studied in animal models prior to World War II and demonstrated to be an antagonist to morphine. Wikler et al[38] showed that administration of nalorphine to morphine-dependent subjects not only failed to produce euphoria but precipitated a violent withdrawal syndrome. Interest in nalorphine increased dramatically in 1954 when Lasagna and Beecher accidentally discovered its analgesic properties.[16] Although side effects ultimately made nalorphine unusable as an analgesic, it provided the first indication that a potent analgesic might be nonaddictive.

Subsequent research showed that nalorphine produces a limited amount of analgesia and respiratory depression (it is a morphine-like *partial* agonist), but it also produces some effects (for example, hallucinations) that are distinctly not morphine-like. In 1967, Martin proposed a two-receptor model to explain these unique properties.[18] He proposed that morphine and nalorphine produce their agonist effects by interacting with separate receptors. Nalorphine acts as an antagonist because it also has binding affinity (but no activity) at morphine receptors.

The simple two-receptor model has given way to a much-discussed three receptor model.[19] Briefly, each receptor subtype is thought to mediate different opioid effects:

(1) Mu receptors are thought to be involved in classic morphine-induced analgesia, respiratory depression, physical dependence, etc. Recently, Pasternak[24] has presented evidence that analgesia may be mediated by a subset of high-affinity (mu-1) receptors, and respiratory depression may be due to low-affinity (mu-2) receptors (compare meptazinol).

(2) Kappa receptors are thought to mediate analgesia by a different mechanism and may account for the analgesic effects of drugs like pentazocine, butorphanol, and nalbuphine. Relatively pure kappa agonists (like bremazocine—not discussed here) produce sedation and may induce diuresis; they do not produce respiratory depression and will not substitute for morphine in a morphine-dependent animal.

(3) Sigma receptor agonists cause mania, hyperpnea, and mydriasis in the dog. Opioids that cause dysphoria and hallucinations (pentazocine, nalorphine) are thought to activate these receptors. One school of thought currently holds that these are not opioid receptors at all. Binding of sigma agonists corresponds quite well to the binding of phencyclidine and its congeners ("angel dust," ketamine), giving rise to the intriguing notion that these drugs may all produce hallucinations by a common mechanism!

Hypothetical receptor interactions of some clinically used opioids are given in Table 2. Note that each opioid may be an agonist, a partial agonist, or an antagonist at each receptor. The agonist-antagonists may be grouped broadly into those producing analgesia at mu receptors

Table 2. *Hypothetical Receptor Interactions for Various Opioids*

DRUG	RECEPTOR mu	 kappa	 sigma
Morphine	Agonist	Agonist	—
Buprenorphine	Partial agonist	—	—
Dezocine	Partial agonist	—	—
Meptazinol	Partial agonist	—	—
Pentazocine	Antagonist	Partial agonist	Agonist
Butorphanol	Antagonist	Partial agonist	Agonist
Nalbuphine	Antagonist	Partial agonist	Agonist
Naloxone	Antagonist	Antagonist	Antagonist

and those acting at kappa receptors. Partial agonists at the mu receptor (for example, buprenorphine) have high affinity but limited efficacy at morphine receptors. They produce morphine-like effects but have shallow dose-response curves. Because they bind strongly, they may displace pure agonists like morphine and therefore act as antagonists. The kappa type agonist-antagonists (for example, pentazocine) also act as competitive antagonists at the mu receptor, but they produce their analgesic effects at kappa receptors.

The agonist (that is, analgesic) potencies of these agents are not related in any consistent way to their antagonist potencies. Neither agonist *versus* antagonist potency nor putative receptor interactions have proved to be good predictors for patient acceptance or abuse liability.[13]

NEW DRUGS

Meptazinol

This drug may be classed with the agonist-antagonist opioids, but it appears to produce its effects by both opioid and nonopioid mechanisms. It acts as an analgesic in animals and man, is naloxone reversible, and has opioid antagonist properties. In vitro binding and some whole animal studies[34] suggest that meptazinol interacts selectively with mu-1 receptors (vide supra), but probably not with kappa or sigma receptors. In addition to its opioid properties, meptazinol appears to produce analgesia in the mouse by a central cholinergic effect. It is not clear how the clinical pharmacology of this drug may be ascribed to its cholinergic properties or to what extent opioid and nonopioid mechanisms are linked. Thus far, antagonism of the analgesia by central anticholinergic drugs (for example, scopolamine) has not been demonstrated in man.

Meptazinol is well absorbed after oral, rectal, and intramuscular administration. It is quite fat soluble and undergoes rapid redistribution and slower elimination (T1/2 = 1.6 hours). The drug is rapidly cleared by hepatic biotransformation and is subject to extensive first-pass metabolism. Meptazinol crosses the placenta and is secreted in breast milk, but unlike many opioids, it is rapidly eliminated in the neonate.[7]

The drug is an effective parenteral analgesic in a wide variety of acute pain states including postoperative pain, labor pain, renal colic, and cancer pain. It has been given intermittently, by continuous infusion, and in an on-demand analgesia system. After intramuscular administration, peak analgesic effects occur between 30 and 60 minutes, and the duration (in postoperative pain) is about 4 hours. Analgesic potency measured on the basis of peak effect is similar to meperidine, and the recommended dose range is 60 to 100 mg intravenously or intramuscularly.

Selective action at mu-1 receptors implies analgesia without respiratory depression, and meptazinol has partially lived up to that promise. In concious volunteers, meptazinol produced very little respiratory depression in comparison with morphine or pentazocine.[14] Intramuscular injection of 100 mg per 70 kg caused no change in the ventilatory response to CO_2, although resting end-tidal CO_2 increased slightly. In halothane-anesthetized patients, meptazinol caused dose-related decreases in respiratory rate and elevations in end-tidal CO_2. Naloxone (0.4 mg intravenously) reversed this effect, indicating that it is probably an opioid effect. It seems that the small amount of respiratory depression produced by meptazinol may become significant in the presence of other central nervous system depressants.

The most frequent side effects of meptazinol are nausea and vomiting (approximately 9 per cent in postoperative pain), sedation, and dizziness. Interestingly, meptazinol produces no consistent effect on the pupil. Perhaps because of its cholinergic action, meptazinol has not been reported to produce constipation.

There are almost no reports of euphoria, dysphoria, or hallucinations with this drug. One study by Kaiko et al[15] compared three doses of morphine with three doses of meptazinol for acute postoperative pain in cancer patients. Both drugs produced dose-related analgesia (as measured by ordinal pain scores), but only morphine produced dose-related elevation in mood. Meptazinol actually had a *negative* effect on mood scores, and patient acceptance of the drug was much lower than for morphine.

Evans et al[9] report that meptazinol is an opioid antagonist with 1/20 to 1/40 the potency of nalorphine in animals. The analgesic potency and agonist-antagonist ratio are therefore similar to those of pentazocine. Meptazinol precipitates abstinence in opioid-dependent animals, although this has not been demonstrated in man. Chronic high doses of meptazinol produce a low level of physical dependence. Tolerance occurs to the analgesic effects in rats and monkeys, but this tolerance is less marked than that observed with morphine.

In summary, meptazinol is an effective analgesic with a very low potential for producing respiratory depression and a low probability of diversion and abuse. Favorable kinetics in the newborn indicate that it may have a role during labor and delivery. Its major limitation may be its lack of positive effects on mood and possibly a low rate of patient acceptance.

Dezocine

This compound is a bridged aminotetralin that appears to act as a mu partial agonist (like buprenorphine). As of this writing, the drug has completed phase III clinical trials. In animals, dezocine is a potent analgesic and antagonist. It does not maintain morphine-induced physical dependence and precipitates severe abstinence in morphine-dependent monkeys.[17]

Dezocine is well absorbed after oral or intramuscular administration. It undergoes extensive distribution and is rapidly eliminated by conjugation in the liver. The elimination half-life is 3 hours in man.

The drug has been studied in a variety of pain models and was generally found to be equipotent or slightly less potent than morphine. Intramuscular or intravenous doses of 10 to 20 mg are effective for moderate to severe pain.[8,10] The duration of analgesia is similar to that of morphine, although the onset may be more rapid. In monkeys, the analgesic effect of dezocine is only partially antagonized by naloxone.

Dezocine has greater intrinsic activity than the other available mu partial agonists. Doses up to 30 mg per 70 kg produce the same respiratory depression as equianalgesic doses of morphine.[39] When the dose of dezocine is increased, respiratory depression is said to reach a plateau,[26] although we have seen apnea in a healthy individual given 0.5 mg per kg intravenously (Rosow, unpublished observations). Dezocine is similar to pentazocine, butorphanol, and nalbuphine in that it has a limited ability to decrease the minimum alveolar concentration (MAC) of volatile anesthetics. Rowlingson et al[28] have found that dezocine reduces cyclopropane MAC by 50 per cent in rats. This is the largest reduction thus far described for an agonist-antagonist opioid.

Side effects are similar to other drugs in this class: nausea and vomiting occur in 16 per cent of postoperative patients; sedation and dizziness occur, but dysphoria and hallucinations have not been described. The smooth muscle effects of dezocine should be less than morphine, but in a recent perioperative study we found 3 of 28 patients (11 per cent) had urinary retention requiring catheterization (Rosow, unpublished observations).

In doses up to 30 mg, dezocine is perceived as morphine-like by postaddicts, but their preference for the drug does not increase as the dose is raised. Physical dependence could not be demonstrated unequivocally in monkeys, and the data suggest that the drug may have a very low dependence liability.

In summary, dezocine is a strong agonist and antagonist that appears similar to buprenorphine. Its intrinsic activity is clearly greater than that of buprenorphine and so is its potential for producing morphine-like side effects. Dezocine seems to share buprenorphine's high affinity for mu receptors and some of its resistance to reversal by naloxone. The low level of physical dependence is encouraging, but it requires substantiation by clinical experience.

OPIOID PEPTIDES

Since the discovery of the enkephalins and endorphins, there have been a variety of preclinical and clinical investigations of opioid peptides as analgesics. In general, the results have been disappointing, particularly in the case of the pentapeptides, which undergo extremely rapid hydrolysis by plasma peptidases. The longer peptide, beta-endorphin, has been used successfully to produce analgesia by the epidural route. Two other avenues of approach have been tried: (1) enkephalin analogues have been made relatively resistant to enzymatic cleavage by the incorporation of d-amino acids; and (2) drugs have been tested that specifically inhibit enkephalin-degrading enzymes.

Metkephamid and DADL

Metkephamid (L-tyrosyl-D-alanylglycyl-L-phenylalanyl-N^2-methyl-L-methionamide) and DADL (D-ala, D-leu enkephalin) are congeners of methionine and leucine enkephalin, respectively. These peptides are thought to be selective for yet another subset of opioid receptors termed delta. In animals, these peptides produce analgesia but relatively little respiratory depression, tolerance, or physical dependence.

Bloomfield et al[4] completed a study of intramuscular metkephamid in postpartum episiotomy pain. Metkephamid (70 and 140 mg) was compared with 100 mg of meperidine and placebo under double-blind conditions. The smaller dose was ineffective, but the larger dose compared favorably with meperidine. Metkephamid produced a greater intensity of analgesia, and the duration of action was greater than 6 hours. Metkephamid caused a high frequency of minor side effects including dry mouth, eye redness, "heavy limbs," tingling sensations, and nasal stuffiness. Nausea was not prominent, and neither respiratory depression nor unpleasant mental effects were reported.

Yaksh[40] showed that both mu and delta mechanisms are involved in the production of spinal opioid analgesia. Both metkephamid and DADL produced dose-related, naloxone-reversible analgesia after epidural administration in the monkey. Interestingly, monkeys made tolerant to epidural morphine did not become cross-tolerant to epidural metkephamid or DADL. Yaksh reported one cancer patient who developed high-grade tolerance to epidural morphine but remained responsive to epidural DADL.

Thiorphan and Bestatin

An alternative to administering exogenous enkephalin analogues is to administer chemicals that inhibit the enzymatic breakdown of endogenous enkephalin. Thiorphan (a carboxypeptidase inhibitor) and bestatin (an aminopeptidase inhibitor) were both shown to produce analgesia in cancer patients.[21] Combining the two inhibitors produced better analgesic effects than either alone. For the combination, the average onset of analgesia was 20 minutes and the average duration was 18.1 hours.

CONCLUSION

The real "news" in analgesia may be in the innovative ways we are learning to use analgesics for acute and chronic pain. So, why the emphasis on new drugs?

The properties that made morphine and meperidine "gold standards" yesterday do not necessarily make them well-suited for our clinical applications today. Demand analgesia, epidural analgesia, and high-dose opioid anesthesia ask rather different things from an analgesic. Most of the newer opioids are improvements with respect to specificity and pharmacokinetics, and most were created with a specific application in mind.

With the possible exception of the new peptides, the drugs discussed here are variations on drugs we know pretty well: They are fentanyl-like agonists, agonist-antagonists, new versions of naloxone, etc. In my opinion, this reflects the current state of the analgesic "art." In 10 or 20 years, my article on analgesics may need to dwell on other topics; for now, the opioid alkaloids continue to play a dominant role in the therapy of pain.

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What's New in Skeletal Muscle Relaxants and Their Antagonists?

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THE NEW NONDEPOLARIZING RELAXANTS

Drug companies prefer to develop compounds that have market appeal. When designing a new relaxant, the chemist must first comprehend, then satisfy, the needs of the clinician. New agents should offer additional clinical options that broaden the scope of services that can be provided safely to patient and surgeon.[130] In the field of nondepolarizing neuromuscular blocking agents (NMBAs), the major requests have been for agents with a shorter duration of action than the traditional curariforms, for agents with a rate of onset comparable with that of succinylcholine, and for agents devoid of cardiovascular side effects.

Atracurium and vecuronium are now in the process of altering clinical practice. Although pancuronium is still the popular choice, atracurium and vecuronium sales continue to expand, with sales audits suggesting a real growth in overall usage of neuromuscular blocking agents in the clinic. To be previewed in this chapter are those neuromuscular blocking agents promising enough to be selected for present and future clinical trials, having names with which we are unfamiliar. Some have yet to receive a name and can be referred to only by their number; they may have been supplanted even before reaching the anesthesiologist.

DURATION OF ACTION

Classification

The traditional curariform agents have a relatively slow onset of action (4 to 10 min) and an expected duration of action (45 to 70 min). As shown in Figure 1, the classification of Savarese and Kitz[130] has been expanded by the Editor to accommodate the new neuromuscular blocking agents likely to enter anesthetic practice, adding ul-

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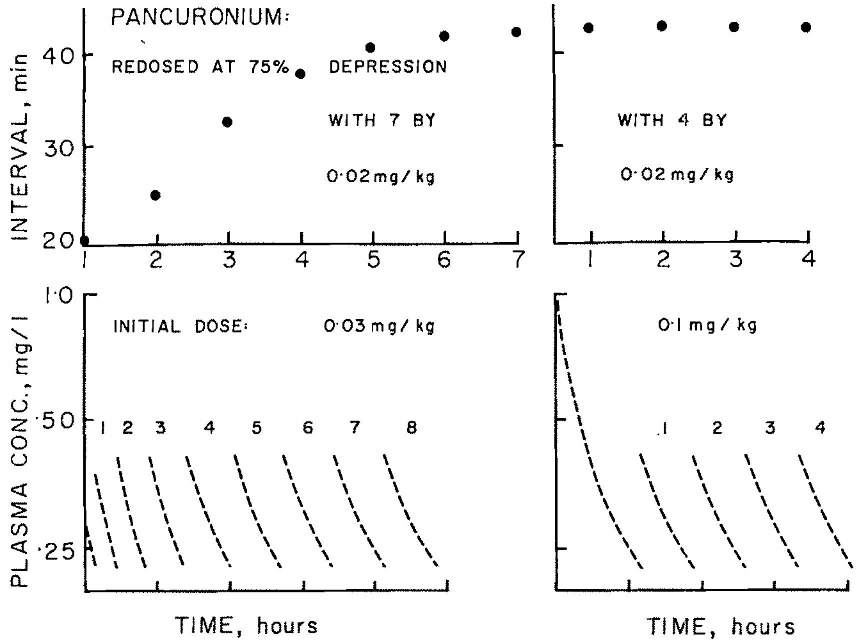

Figure 1. A classification of the neuromuscular blocking agents (NMBAs) according to the time-course of paralysis. (*Adapted from* Savarese JJ, Kitz RJ: Does clinical anesthesia need new neuromuscular blocking agents? Anesthesiology 42:236–239, 1975; with permission.)

trashort and short-duration categories to the now standard intermediate and long-acting groupings. The more rapid and complete the return of muscle tone, the less likely are problems due to continuing postoperative paralysis. The disadvantage of rapid spontaneous recovery will be seen by the unwary; following an intravenously injected (bolus) dose, good surgical relaxation can become most inadequate in a very few minutes.

Surgical Relaxation

Data on the duration of action are reported differently by various authors, but many give the time interval between administration of a single intravenous dose and spontaneous recovery of the twitch response to 25 per cent of its control height, i.e., 75 per cent twitch depression, a value thought to reflect the duration of useful surgical relaxation. This interval is dose dependent but not necessarily in a linear fashion: the long-acting agents can show marked prolongation of surgical paralysis at increased dosage, an effect attributable to the shape of the concentration-time curve in the therapeutic concentration range.[138] When the concentration-time curve in this range is steep, spontaneous recovery is rapid.

Table 1 shows the time-course of neuromuscular blockade for

Table 1. *The Time-Course of Paralysis During "Balanced" Anesthesia in Humans: Mean Values*

		TIMES (MIN)			
	DOSE (MG/KG)	*Onset*	*Duration Surgical Relaxation*	*Recovery Index*	REFERENCE
Short-acting Mivacurium	0.08–0.25	2–12*	12–22*	6–7	7, 33, 97, 98, 103, 156
Intermediate-acting Atracurium	0.2–0.6	2–7*	17–45*	10–12	8, 17, 45, 57, 70, 83, 120, 134, 159
Vecuronium	0.04–0.25	2–5*	11–72*	11–72*	7, 17, 28, 59, 62, 70, 83, 72, 117, 120, 124, 159
Long-acting Doxacurium	0.23–0.48	3–10*	28–121*	24–96*	10, 67, 75, 87, 100, 109, 125
Pipecuronium	0.03–0.07	5–10*	32–85*	36–?	4, 24, 29, 112, 148

*Dose-dependent

each of the new NMBAs administered as an "intubating dose," i.e., at about twice the dose that depresses the twitch response by 95 per cent, the ED95. It is possible to intubate the trachea with the ED95 dose of a neuromuscular blocking agent, but adequate relaxation takes longer to develop than with a larger dose. It should be emphasized that most studies report the intensity of paralysis for the adductor pollicis muscle. In man, this muscle is more sensitive to the effects of neuromuscular blocking agents than either the vocal cords[71] or the diaphragm; the latter is blocked earlier and less completely, and recovers more quickly than the thumb muscle.[31,32,51,74] Orbicularis oculi shows a slower onset of blockade than does adductor pollicis.[86]

Pharmacokinetics

Spontaneous recovery from blockade is related to NMBA plasma concentrations. These concentrations decrease to nontherapeutic levels owing to both redistribution and clearance. Redistribution seems to be a major factor with the new steroidal neuromuscular blocking agents from Organon, whereas a rapid clearance underlies the short duration of action with the Burroughs-Wellcome derivatives of isoquinoline, atracurium, and mivacurium. All agents are cleared via the liver and kidneys, but drugs that rely wholly on organ function for elimination are likely to show prolonged action in the presence of hepatic or renal pathophysiology. Enzymatic degradation by pseudocholinesterase occurs with several of the isoquinoline derivatives; atracurium is affected by carboxylases and Hofmann elimination.

ONSET OF ACTION

Most anesthesiologists would like their neuromuscular blocking agent to have a rapid onset time, recognizing that no drug can act more quickly than the circulation time allows.[82] The long- and intermediate-duration drugs now in use have had their dosing altered in attempts to shorten the 3 to 5 minutes required for the development of adequate muscular paralysis: chief among these are the use of markedly increased dosage and the prior administration of a fraction of the total dose. The latter, often designated as the priming principle, can involve administration of an ED5 or ED10 of the same or another neuromuscular blocking agent;[104,132] this dose is best given some 4 minutes before the main dose.[145] Objections to this priming technique include its unreliable and unpredictable production of relaxation,[17,157] frightening subjective changes experienced by the patient, and the risk of aspiration.[55,110] The author suspects that an appropriate priming dose is that shown in Table 1, inducing anesthesia as soon as the patient begins to drop a raised limb.[5] The need for the priming technique will diminish with the advent of new neuromuscular blocking agents with shorter onset times.

Rapid onset is usually associated with a short pharmacodynamic half-life (Bevan DR, personal communication), i.e., the intensity of paralysis both waxes and wanes rapidly after a single dose. The development of large numbers of new compounds has allowed new insights into the action of neuromuscular blocking agents; the new drugs seem to reverse the trend toward synthesis of increasingly potent agents. In any congeneric series, the high potency agents have a longer onset time (Bowman WC, personal communication). Thus, when a cloud of low-potency neuromuscular blocking agent molecules is carried to the muscle by the circulation, they can flood the receptors, active and otherwise. Doses of some experimental compounds at one to three times the ED95 then produce intense blockade in animals, at rates comparable with those of succinylcholine. The release of these new agents for human studies is awaited with interest.

DOSE RESPONSE

The dose-response relationships of the neuromuscular blocking agents are developed separately for their administration by a single rapid intravenous (bolus) dose or by infusion; potency ratios may differ with these two types of administration for pharmacokinetic reasons.[138] The usual dose-response curves are based on the peak intensity of effect following a single dose per patient. With the long-acting agents, experimental design is often simplified by administering serial doses to the same patient, the cumulative dose technique. The cumulative method overestimates the doses of atracurium and vecuronium;[62,70,117] its use appears suitable for the long-acting neuromuscular blocking agents. Halothane appears to alter minimally the dose-response curves for vecuronium;[117] enflurane and isoflurane produce a dose-related shift to the left of the dose-response curve.[124] Potentiation of atracurium is seen with enflurane[124] and isoflurane.[122] Similar potentiation of the newer neuromuscular blocking agents is to be expected.[88,100,156]

CUMULATION

Multiple doses of vecuronium showed some minor "cumulation," defining the term as a time-related increase in duration of action for a fixed incremental dose. Cumulation was reported for pancuronium when administered in increments of 0.02 mg per kg upon spontaneous recovery to 75 per cent depression.[56] Simulation following an initial dose of 0.03 mg per kg shows such cumulation but not when following pancuronium, 0.1 mg per kg (Fig. 2), confirming the modeling reported by Norman.[115] The lack of cumulation for atracurium and high-dose pancuronium is due to superimposition of the incremental dose curve on the same part of the initial dose curve, regardless of whether the latter is in the distribution or elimination phases. With low-dose pancuronium, and to a minor degree with prolonged vecuronium administration, the initial increments add to concentrations on the distribution phase; later increments are added at the less steep slope of the elimination phase, so that the duration of effect from a dose increases, i.e., the observation of cumulation depends on the prior dosing schedule.

INFUSIONS

Pharmacokinetics

When a drug is infused at a fixed rate, it takes more than four half-lives to reach steady state. As a corollary, adjustments in the infusion rate are more rapidly effective with drugs having a shorter half-life. A true steady state is achieved when the amount of drug infused is equal to that being cleared by the body. With the neuromuscular blocking agents, complex dosing patterns are not necessary to achieve an early plateau in plasma concentrations. Both a steady state and a plateau are associated with a constant intensity of blockade, but a plateau will probably require further adjustment in the dosage pattern for this to continue.

Bolus Plus Infusion

If an appropriate bolus dose is injected at the same time as the infusion is started, there is an immediate peak in the plasma concentrations during the onset of blockade. Later, the increase in plasma

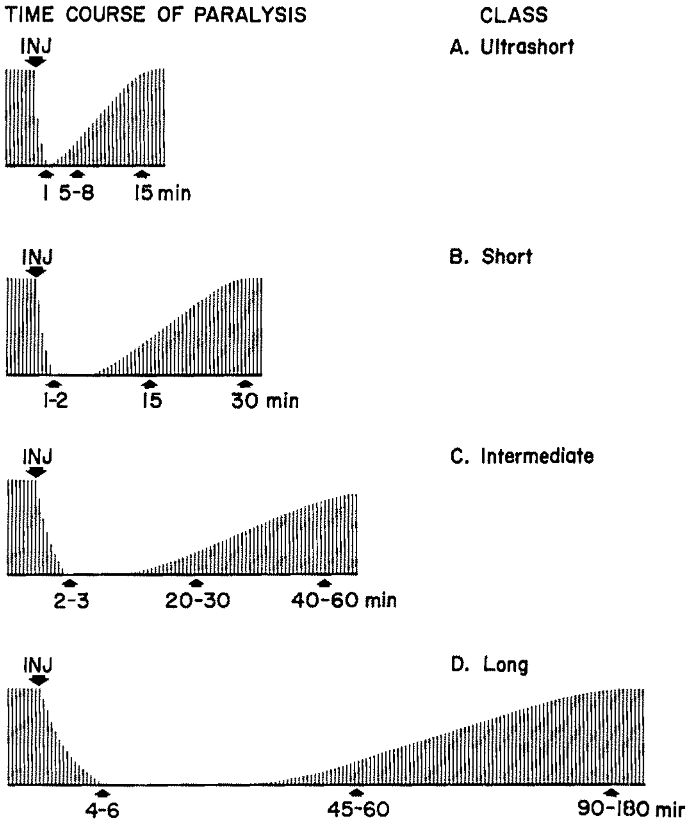

Figure 2. Simulation of the duration of surgical relaxation with multiple doses of pancuronium, repeated when there would have been 75 per cent twitch depression. The dosing interval (*above*) remains constant when the initial dose is large, ie, the observation of cumulation is dose-dependent. (*From* Shanks CA: Simulating the time-course of clinical paralysis. Int J Clin Monitor Comput, in press; with permission.)

concentrations due to the infusion is matched by the decreasing values from the bolus, producing an early, but not immediate, plateau. The high concentrations following an ED95 dose quickly introduce relaxant into the "effect compartment," where they are maintained during the plateau. The longer the interval between the bolus dose and the start of the infusion, the greater the additional dose of relaxant necessary to "catch up," either as part of a larger initial bolus or with an increase in the later infusion rate. The bolus plus infusion technique has both the rapidity of blockade onset from the bolus and the control of intraoperative blockade with the infusion; the regimens have been reviewed elsewhere.[138]

Table 2 shows average infusion rates that are associated with 90 per cent twitch depression with the new neuromuscular blocking agents. Monitoring the evoked twitch responses allows (reacting slowly!) changes to be made in the infusion rate for maintenance of adequate surgical relaxation, and timing of discontinuation of the in-

Table 2. *Relaxant Administered by Infusion: Mean Values*

	DOSE (μG/MIN/KG)	RECOVERY INDEX (MIN)	REFERENCE
Mivacurium	7.6–8.3	5–7	1, 7, 20, 119
Vecuronium	1.0–1.7	13–26	7, 27, 136, 144
Atracurium	4.3–8.4	4–11	19, 41, 52–54, 68, 76, 78, 102, 114, 129

fusion as surgery nears completion. Several groups of workers developed closed loop systems for automatic control of blockade, using feedback between either an evoked electromyogram or force transducer and an infusion pump.[53]

Atracurium Infusion

Atracurium has been administered by continuous infusion during many types of prolonged surgery, both in adults[41,52,54,58,68,102,114,129] and in children.[19,76] If atracurium is diluted for the infusion, normal saline is preferred, as spontaneous degradation occurs more rapidly in lactated Ringer's solution.[60] During balanced anesthesia, 90 to 99 per cent twitch depression is maintained by rates that average 6 to 9 μg per kg per min (see Table 2). The dosage is not different when total intravenous anesthesia with midazolam and alfentanyl is compared with fentanyl and nitrous oxide.[114] The potent inhalation agents reduce the dosage requirements,[19,54,76] but there is considerable overlap. Dosage requirements are not affected by age.[41] Atracurium infusion requirements are decreased during the anhepatic phase of liver transplantation[58] and during hypothermic cardiopulmonary bypass.[48,65]

Laudanosine

There is concern about the influence of renal failure on the elimination of a major metabolite of atracurium, laudanosine;[57,149,154] its avoidance is suggested for patients in renal failure who require prolonged relaxation. This may also be true of patients with hepatobiliary dysfunction.[152] Atracurium infusion is useful in the intensive care unit, administered in greater dosages than those shown in Table 2. Atracurium enables prolonged relaxation in these patients to be followed by the usual rate of recovery, despite circulatory, renal, and/or hepatic dysfunction.[78,153,162] Two of these infusion studies include reports of one patient with renal failure and subsequent seizure activity: the fear is that accumulation of the metabolite, laudanosine, might be implicated. In one case, trauma was followed by extensive intracerebral pathology. In the other, the patient developed generalized twitching; two hours after the last dose of atracurium was given, the plasma laudanosine level was 0.74 μg per ml, less than half the concentration associated with convulsions in dogs.[30] It would appear that laudanosine is unlikely to cause seizures clinically. It remains to be seen whether there is a problem when laudanosine production increases anesthetic requirement.[139]

Vecuronium Infusion

Vecuronium infusion requirements average between 1.0 and 1.5 μg per kg per min (see Table 2); they are not affected by previous succinylcholine[39] but should be reduced for elderly patients[40] and during hypothermic cardiopulmonary bypass.[48,65] Requirements are reduced by halothane,[144] enflurane, and isoflurane.[27] The suggestion that halothane increases neuromuscular sensitivity to vecuronium-induced blockade has not been confirmed.[136]

Mivacurium Infusion

A continuous infusion of mivacurium averaging 6 to 8 μg per kg per min during balanced anesthesia produces almost total depression of the twitch response.[1,7,20] Post-infusion recovery data are shown in Table 2; its time-course is more rapid than with the neuromuscular blocking agents of the intermediate group.

CARDIOVASCULAR SIDE EFFECTS

Many anesthesiologists use the cardiovascular side effects seen following the initial administration of neuromuscular blocking agents. Some combine pancuronium with a high-dose narcotic technique and dislike the narcotic-induced bradycardia unmasked when vecuronium is substituted for pancuronium. Others intubate the trachea during relaxation provided by atracurium, alcuronium, or metocurine, timed so that the cardiovascular responses to intubation correct the hypotension due to the neuromuscular blocking agent, preferring this technique over the need for lidocaine or beta-adrenergic blockade. The cardiovascular response to intubation is less marked when fentanyl is given at induction and short-lived with atracurium and vecuronium.[94]

Clinicians who would like all their drugs to have a "clean" cardiovascular profile will have a longer wait for this development in the other classes of intravenous drugs than in neuromuscular blocking agents. Vecuronium is now the standard against which all the others will be measured; it is administered at many times the ED95, at doses of 0.25 mg per kg or more, without cardiovascular changes.[59,72,108] There are two long-acting neuromuscular blocking agents now in clinical trials that lack cardiovascular effects: pipecuronium and doxacurium.[4,29,90,109,143,146,160] Still in animal trials are two more that may also fit this category, ORG 9273 and ORG 9426. Rapid injection of the short-acting mivacurium[66,128] and the intermediate-duration atracurium[134] has the potential to produce hypotension. The upper limits to the amount of vecuronium, doxacurium (BW A938U), or pipecuronium that can be administered safely to the well-ventilated patient have yet to be determined.

ANAPHYLACTOID REACTIONS

Life-threatening anaphylactoid reactions to muscle relaxants commonly occur in patients who were not previously exposed to the neuromuscular blocking agent;[63] these reactions are not related to additives or preservatives. Fifty per cent of subjects who experience anaphylaxis to a relaxant can be sensitive to one or more neuromuscular blocking agents; metocurine and atracurium are highly cross-reactive with IgE antibodies in allergic patients unexposed to these drugs.[81] These reactions should not be confused with the dose-related release of histamine.

INDIVIDUAL RELAXANTS

Ultrashort Duration: ORG 7617, ORG 9616

At a recent meeting, Organon unveiled four new compounds that were tested in several animal species (Savage DS, personal communication). These are one third to one tenth less potent than vecuronium but with a shorter onset time. Their rapid offset of action is due to redistribution rather than clearance; they redistribute extensively, especially to the liver, and are largely excreted in the bile.

These two neuromuscular blocking agents are selected for their uniquely short time-course of paralysis. They do not offer the cardiovascular stability of vecuronium: ORG 9616 administration is associated with elevations of heart rate and blood pressure, ORG 7616 with hypotensive episodes. In equipotent doses, their onset time is identical with that of succinylcholine. Their duration is also equivalent to succinylcholine in the cat and monkey but is slightly longer in the dog and pig.

Short Duration: Mivacurium, ORG 9273, ORG 9426

Mivacurium

This agent (BW B1090U) has a very short duration of action in monkeys;[131] it has since been introduced into clinical trials. Doses in excess of 0.1 mg per kg abolish the twitch responses in 2 to 3 minutes, followed by 15 to 20 minutes of surgical relaxation; at these doses spontaneous recovery is almost complete in 30 minutes.[9] Such doses may produce brief decreases in arterial blood pressure, associated with elevations of plasma histamine levels. Even larger doses were reported to allow good to excellent intubating conditions within one minute.[127] Cardiovascular changes are less after a second identical dose, or after slower bolus administration; the margin of safety of mivacurium is similar to that of atracurium.[128] Its use in outpatient procedures may offer significant advantages over succinylcholine, both in the recovery room and 24 hours later.[103]

Although the potent inhalation agents may potentiate mivacurium,[156] the time sequence of anesthesia would make this interaction unlikely on the initial dose. Following a dose of 0.25 mg per kg, mivacurium provides good intubating conditions in 90 to 120 seconds, with or without priming, during induction of light anesthesia with intravenous drugs.[126]

It is hydrolyzed by human plasma cholinesterase at about 90 per cent of the rate of succinylcholine,[35,131] suggesting that its duration of action would not be greatly prolonged in the presence of a heterozygous atypical enzyme: two such cases have already been reported.[156] As shown in Table 3, its removal by cholinesterase confers a high clearance and short elimination half-life.[43]

ORG 9273 and ORG 9426

Of the four new agents from Organon, two could be classified as short-acting, the animal studies predicting that their duration will be less than that of vecuronium but with the same cardiovascular stability. Their advantage is mainly that their onset time is half that of vecuronium.

Intermediate Duration: Atracurium, Vecuronium

Dosage

Atracurium and vecuronium are both intermediate-duration neuromuscular blocking agents (see Fig. 1) despite considerable differences in their disposition. Their speed of onset is less than that of succinylcholine.[79,133] Approximately 3 minutes following administration of vecuronium, 0.05 mg per kg, or atracurium, 0.2 mg per kg, the trachea can be intubated; these doses provide surgical relaxation for about 15 minutes.[8,59] Each multiple of these ED95 doses provides approximately 16 minutes further.[59,72] Increasing the dose will reduce the time interval between the dose and full neuromuscular blockade; increase in atracurium beyond 0.4 mg per kg is more likely to be associated with cardiovascular changes.[8,133] For vecuronium, one study sets the limit of reduction of this time interval at three times the ED95. At doses of 0.15 mg per kg and greater, the onset time was no shorter, with doses as high as eight times the ED95.[28] Another group found progressive reduction to 100 seconds onset time when doses of vecuronium, 0.4 mg per kg, were used.[72] Although there is not complete agreement between studies, equipotent doses of the two drugs have equivalent times of onset.[83] Rapid sequence endotracheal intubation can be successfully accomplished at one minute with either atracurium, 1.5 mg per kg, or vecuronium, 0.25 mg per kg.[99] When administered on a weight basis, obese patients receiving vecuronium had prolonged recovery; this was not seen with atracurium.[159]

The rapid spontaneous recovery with these agents has led to increasing use of twitch monitoring. Clinicians who lack the monitors to measure the evoked responses during surgery frequently count the number of twitches with a train-of-four (4 stimuli in 2 seconds, at intervals of not less than 10 seconds). With atracurium, all four can first be palpated when blockade recovers to 75 per cent twitch depression;[80] with vecuronium, visualization is less sensitive.[116]

Histamine

Although vecuronium does not alter serum histamine when administered,[11] atracurium does.[8] Pretreatment with cimetidine and chlorphenhydramine abolishes the hemodynamic response to atracurium, 0.6 mg per kg but provides incomplete protection against higher dosage;[134,135] the best protection is to administer the atracurium over a period of 75 seconds. The author can see no reason to use doses of atracurium in excess of 0.4 mg per kg.

Pharmacokinetics

The pharmacokinetics of atracurium and vecuronium are shown in Table 3. The smaller distribution volume of atracurium is reflected in a plasma concentration-time curve that is almost monoexponential, so that its rate of recovery is predictable for any one patient, related to the elimination half-life.[49] This contrasts with vecuronium, which relies on redistribution for its intermediate duration of action.

Renal Failure

Unlike the alterations to the pharmacology of the long-acting agents that are seen in renal failure, there are no major changes in the kinetics and dynamics of atracurium[44,84,57] and vecuronium.[14,15,56,101,105] The topic of laudanosine and its potential to induce seizure activity is dealt with in the infusion section.

Table 3. *Pharmacokinetics of the New Neuromuscular Blocking Agents: Mean Values*

	VOLUME, STEADY STATE (L/KG)	CLEARANCE (ML/MIN/KG)	HALF-LIFE (MIN)	REFERENCE
Mivacurium	0.2	55	17	43
Atracurium	0.14–0.28*	5.1–6.1	17–21	34, 42, 44, 57, 45, 149, 155
Vecuronium	0.22–0.28	3.6–6.7	24–92	14, 36, 56, 96, 101, 105, 121, 142
Pipecuronium	0.31	1.8–2.5	127–207	23, 160

*Distribution volume, area

Hepatic Failure

Liver failure makes little difference to atracurium kinetics[34] or dynamics,[140] even when acute hepatic failure is combined with acute renal failure.[155] The liver exerts a major influence on the disposition of vecuronium. The initial dose of vecuronium, 0.1 mg per kg, has a shorter duration of action in patients with esophageal varices and liver dysfunction;[13] vecuronium, 0.2 mg per kg, has a significantly longer duration of action in cirrhotics.[85] This prolongation of effect is related to the reduced clearance and greater elimination half-life.[95] There are similar effects on vecuronium dynamics and kinetics in patients with cholestasis.[96]

Mothers and Babies

Both agents were used to provide surgical relaxation for cesarean section, without apparent changes in Apgar or other indices of neonatal condition. Little of either neuromuscular blocking agent crosses the placenta, in amounts unlikely to be of clinical significance.[42,47,64] Recently, several authors reviewed the clinical pharmacology of these agents in neonates, infants, and children; both agents were found to have effects similar to those reported for adults, perhaps with a slightly greater interindividual variation.[77,106,113]

Myasthenia Gravis

Considerable variations in dose requirements also occur in patients with treated myasthenia gravis, in which both agents were used safely.[12,21] This variability is related to the intensity of the disease, the residual effects of anticholinesterase medication, and the choice of anesthetic technique. Evoked twitch response recording simplifies initial and subsequent dose requirements for myasthenic patients.

Malignant Hyperpyrexia

Neither agent triggers malignant hyperthermia in malignant hyperpyrexia–susceptible swine.[22,93,161]

Long-Acting Agents: Pipecuronium, Doxacurium

These agents are likely to find ready acceptance by clinicians who must maintain prolonged relaxation in patients with myocardial dysfunction; there are no cardiovascular effects reported in doses up to 1.5 times the ED95.[10,148]

Dosage

Pipecuronium is a steroidal neuromuscular blocking agent and doxacurium (BW A938U) is an isoquinoline derivative. Under balanced anesthesia their ED95s are approximately 25 μg per kg and 35 μg per kg, respectively. As with the other long-acting neuromuscular blocking agents administered at doses in the ED95 range, the time taken to reach maximum blockade may be 10 to 15 minutes; their duration may be 50 to 75 minutes. Doubling these doses will abolish the twitch response in 3 to 4 minutes and increase the duration to 90 to 120 minutes. As with other long-acting neuromuscular blocking agents the potent inhalation agents may reduce the ED95 by as much as 40 per cent.

Pharmacokinetics

Preliminary data suggest that their pharmacokinetics (Table 3) will not differ greatly from the older neuromuscular blocking agents of the same congeneric species. The initial study on pipecuronium kinetics[147] is flawed; plasma concentrations are not reported beyond the first hour. Approximately 5 per cent of doxacurium may be metabolized by plasma (pseudo)cholinesterase. Both doxacurium and pipecuronium are eliminated mainly by the kidney, with lesser removal by the liver. In patients with renal failure, there is reduced clearance of pipecuronium.[137] There are, as yet, no data for doxacurium.

ANTAGONISTS

ANTICHOLINESTERASES

The pharmacokinetics and pharmacodynamics of the anticholinesterases are reviewed elsewhere.[2,37,38,61] Modeling actions of the anticholinesterases in man are complex, as neither the neuromuscular blocking agent nor the anticholinesterase is likely to be at steady state, and both drugs have time-related changes in their intensity of effect on neuromuscular transmission. Hypothetically, the action of the cholinesterase inhibitors can be conceptualized as a dose-dependent finite shift to the right of the relaxant concentration-effect curve.[137] Once this drug interaction is established, then further recovery from paralysis is due to diminishing relaxant effect. Comparing full dose of edrophonium and neostigmine, the former would produce a more rapid shift but of lesser interval.

There is a debate over the need to reverse neuromuscular blockade at the end of surgical procedures, with the conservatives advocating universal administration of an anticholinesterase. Others do not accept this, usually with the caveat that the fractional train-of-four response should exceed 75 per cent. The data for this statement developed from studies with tubocurarine[18] and are yet unconfirmed for the newer agents. Some confusion also arises from the 75 per cent value: this represents 25 per cent depression of the height of the fourth response and differs considerably from the 75 per cent twitch depression desired during surgery. It is not sufficient merely to observe four responses at the end of surgery; even expert observers are unable to estimate adequate spontaneous recovery of the train-of-four by palpation.[150]

EDROPHONIUM

For many years, edrophonium was considered to have too short a duration of action to be useful in reversal of neuromuscular blocking agent–induced paralysis; most clinicians used neostigmine or occasionally pyridostigmine. The lack of interest in edrophonium was based largely on work[89] that commonly used doses totaling 10 to 20 mg. Later workers[16,91] showed that these doses were too small to be effective in some patients, and many studies now report 0.5 to 1.0 mg per kg. The onset of edrophonium is faster than that of neostigmine, but the intensity of effect is less; their relative efficiency depends on the extent to which neuromuscular blockade has regressed spontaneously.[50,89]

Shortly after a large dose of neuromuscular blocking agent, administration of neostigmine cannot reverse blockade.[6] When blockade is profound but not total, neostigmine is slower but eventually more effective.[3,25,26,92,123,163] If the evoked responses are in excess of 10 per cent of their control values, both edrophonium and neostigmine in divided doses was reported to accelerate reversal.[111] Not only was the action of edrophonium studied after single or multiple bolus doses of neuromuscular blocking agents, but it also was examined during or following infusions of neuromuscular blocking agents.[69,92]

4-AMINOPYRIDINE

4-Aminopyridine (not yet approved in the United States) facilitates neuromuscular transmission, and has the ability to antagonize the neuromuscular blocking agents. This facilitatory action is dependent on the presence of calcium ions, increasing their inward flux by blocking the potassium channels of the nerve terminal. This suggests that, on theoretic grounds, 4-aminopyridine should be better when depression of neuromuscular transmission results from a prejunctional defect (e.g., Eaton-Lambert syndrome, aminoglycoside antibiotics).[118] In reversal of blockade, its major use would appear to be when unwanted paralysis is produced by an interaction between some prejunctional factor and a neuromuscular blocking agent. When 4-aminopyridine is administered together with an anticholinesterase, they act synergistically,[107] with the rationale that the former increases acetylcholine release and the latter delays its destruction.

CONCLUSIONS

Although there is probably no "ideal" neuromuscular blocking agent for every anesthesiologist, despite the various lists found in the literature, soon one will be able to select a relaxant specific for the required onset time, duration, and cardiovascular effect. All the new neuromuscular blocking agents will be competitive at the neuromuscular junction, obviating the unwanted side effects of the depolarizing agents and allowing their reversal with an anticholinesterase. With the ultrashort agents, it may become a moot point whether the reversal is largely spontaneous recovery or due to the anticholinesterase. Use of these new short-acting agents may remove a hazard in the recovery room: undetected persistent partial neuromuscular blockade.[151]

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What's New in Local Anesthetics?

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Following the initial use of cocaine as a topical local anesthetic in 1884 by Koller, a number of local anesthetic compounds were synthesized. Basically, two types of chemical agents are clinically useful as local anesthetics, the amino-ester and amino-amide drugs. The amino-ester compounds include procaine, tetracaine, and chloroprocaine, which are still commonly used local anesthetic agents. Chloroprocaine was introduced into clinical practice in the mid 1950s and no new agents of this type have since been made available to anesthesiologists. One of the advantages of the amino-ester agents is their rapid hydrolysis in plasma, which reduces their potential to produce systemic toxicity. This permits the use of relatively high doses and concentrations of agents such as chloroprocaine, resulting in a rapid onset of anesthesia. Unfortunately these agents are somewhat unstable in solution. In addition, paraaminobenzoic acid, a metabolite of these agents, may lead to allergic type reactions.

A major breakthrough in local anesthetic development came with the introduction of lidocaine into clinical use in 1947. This amino amide local anesthetic agent was more stable in solution than the amino-ester agents and generally had a short onset of block and longer duration of activity. Moreover, these agents and their metabolites are rarely implicated in the production of allergic reactions.

Of the currently available local anesthetic agents, all have some advantages and disadvantages. Chloroprocaine, with its rapid onset of action is extensively administered for obstetric epidurals. The short duration of action seen with this local anesthetic contrasts with the long duration of action seen with bupivacaine. Bupivacaine has the added advantage of providing sensory analgesia at relatively low concentrations without producing profound motor blockade. However, bupivacaine has a longer onset of action than the shorter acting agents and has the potential to produce greater problems if a toxic reaction occurs after intravenous administration. Etidocaine also has

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a long duration of action but lacks the separation between sensory analgesia and motor blockade exhibited by bupivacaine. Thus, etidocaine is of greatest use for surgical procedures that require profound motor blockade. Lidocaine, prilocaine, and mepivacaine have very similar local anesthetic properties with a relatively short onset and intermediate duration of action. Systemically, prilocaine is the least toxic of these three agents because of its rapid metabolism and extensive distribution in the body. However, following the use of high doses of prilocaine, methemoglobinemia can develop. Although the potential to produce methemoglobinemia excludes certain patient groups from its use, this condition is easily managed and should not present a problem with a single dose of up to 600 mg. Thus, prilocaine is well suited for use in intravenous regional anesthesia. Lidocaine is the most versatile agent, not only as a local anesthetic in surgery, obstetrics, and dentistry, but also as an antiarrhythmic agent. It is used for epidural and spinal anesthesia as well as for peripheral nerve blocks, infiltration, and topical anesthesia. Even with this wide range of agents available, there is still room for improvement in terms of safety, versatility, and mode of use of local anesthetics.

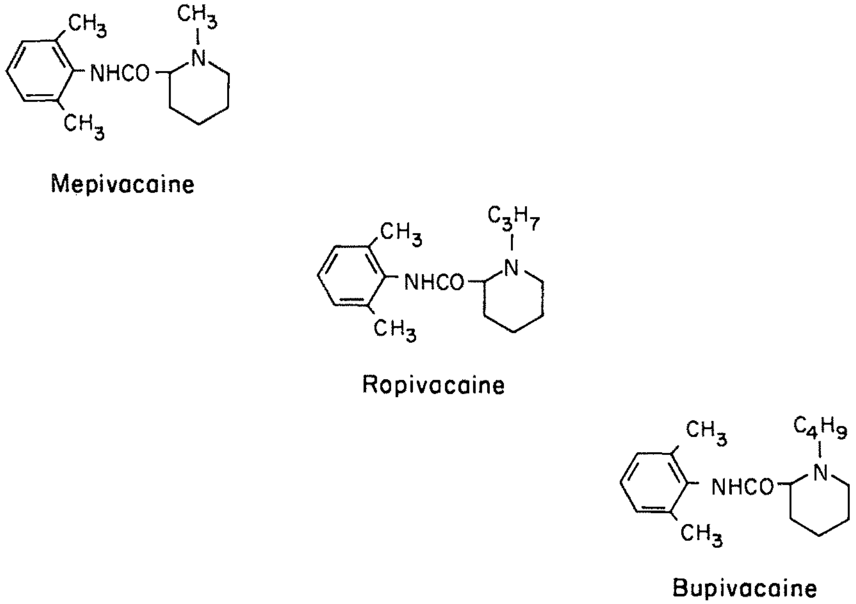
Over the past few years, cases of sudden cardiovascular collapse have been reported after the accidental intravenous injection of bupivacaine.[4] In vitro and in vivo studies indicate that this is due to ventricular tachycardia and fibrillation.[37,45,47,49,61] This would seem to indicate the need for the development of an equally effective, but less toxic, local anesthetic agent of the bupivacaine type.

"NEW" AMINO-AMIDE TYPE AGENTS

Ropivacaine (S-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate) is a new long-acting local anesthetic agent. Structurally, this compound is intermediate to that of mepivacaine and bupivacaine (Fig. 1) but differs from these agents because it is prepared as an isomer rather than a racemic mixture.

Previous animal studies with the isomers of mepivacaine and bupivacaine indicated that the intravenous lethal doses of both agents were greater for the L-isomers, although the convulsive doses were significantly higher only for the L-isomer of bupivacaine.[1] No differences in the nerve blocking capabilities of the D- and L- isomers of either of these agents were observed using an isolated frog sciatic nerve preparation. No differences were observed in the durations of sensory and motor blockade between the isomers of bupivacaine. However, there was evidence to suggest that at higher concentrations (1 per cent), the D-isomer of mepivacaine produced a longer duration of sensory and motor block than both the L-isomer and racemic mixture after sciatic nerve block in the rat.

Preliminary studies showed that the partition coefficient of ropi-



Mepivacaine

Ropivacaine

Bupivacaine

Figure 1. Chemical structures of bupivacaine, ropivacaine, and mepivacaine.

vacaine was intermediate to that of lidocaine and bupivacaine as was its uptake into isolated nerve tissue and extradural fat.[56] Using isolated vagus and phrenic nerve preparations, Rosenberg and Heinonen found that ropivacaine was more potent than bupivacaine or etidocaine for blocking nerve impulses in $A\delta$ and C fibers.[55] They concluded that this agent may be a more effective blocker of pain fibers than bupivacaine and thus a useful drug for regional analgesia. In intact animal preparations, epidural anesthesia using 0.75 per cent and 1.0 per cent ropivacaine solutions produced durations of motor blockade similar to those seen with 0.5 per cent and 0.75 per cent bupivacaine (Table 1).[23] Owing to the difficulty of evaluating sensory block in animals, the question of ropivacaine producing a differential sensory/motor block equivalent to, or greater than, bupivacaine remains to be fully answered. However, data from sciatic nerve blocks and epidural anesthesia in guinea pigs indicate that, in this model, ropivacaine produces an equivalent duration of sensory blockade to that seen with bupivacaine (Table 2).[3]

The acute intraveous toxicity of ropivacaine was investigated in a dog model and compared with lidocaine and bupivacaine.[5] Ropivacaine produced convulsions at a very similar dose to bupivacaine. However, at equivalent doses and plasma concentrations, bupivacaine produced a greater number of deaths and ventricular arrhythmias than lidocaine or ropivacaine. This indicates that ropivacaine has a greater margin of safety between the convulsant dose and lethal dose than does bupivacaine and also that ropivacaine has a

Table 1. *Onset and Duration of Epidural Anesthesia (Motor Blockade) in the Dog**

	ONSET (MINUTES)	DURATION (MINUTES)
Bupivacaine 0.5%	4.1	156
Ropivacaine 0.75%	2.8	103
Bupivacaine 0.75%	2.0	148
Ropivacaine 1.0%	1.7	128

**Adapted from* Feldman HS, Hurley RJ, Covino BG: LEA-103 (Ropivacaine) a new local anaesthetic: Experimental evaluation of spinal and epidural anaesthesia in the dog, and sciatic nerve block in the rat. Anaesthesiology 65:181, 1986.

lower arrhythmogenic potential than bupivacaine (Table 3). Using an in vivo pig model, Reiz and Nath[54] determined the electrophysiologic toxicity ratio for bupivacaine, ropivacaine, and lidocaine to be 15:6.7:1. This ratio was based on the effects of increasing doses of these three agents on the ECG, after their injection into the left anterior descending coronary artery. When these data were corrected for the relative anesthetic potency of bupivacaine to ropivacaine (1.3:1) then the "toxicity" ratio became 1.7:1 (bupivacaine to ropivacaine), indicating that ropivacaine was still less cardiotoxic than bupivacaine. Similar conclusions were also drawn from an in vitro Purkinje fiber/ventricular muscle preparation.[46] Exposure of the Purkinje fiber/muscle preparation to concentrations of bupivacaine and ropivacaine in the perfusion medium, designed to simulate an intravenous bolus injection of local anesthetic, resulted in the Purkinje fiber becoming inexcitable to electric pacing for 4 minutes with ropivacaine and 18 minutes with bupivacaine. The duration of Purkinje fiber/ventricular muscle conduction blockade was 33 minutes for ropivacaine and 48 minutes for bupivacaine. At lower concentrations of drug in the perfusion medium, the depressant effects of ropivacaine on both the Purkinje fiber and ventricular muscle transmembrane action potentials were consistently less than those of bupivacaine.

Based on the currently available data, and assuming these laboratory data are applicable to man, it would appear that ropivacaine is potentially a clinically useful local anesthetic.

Table 2. *Duration of Sensory Anesthesia after Sciatic Nerve Block and Epidural Anesthesia in the Guinea Pig**

	SCIATIC (MINUTES)	EPIDURAL (MINUTES)
Bupivacaine 0.75%	102	65
Ropivacaine 0.75%	134	51

**Adapted from* Akerman B, Sandberg R, Covino BG: Local anaesthetic efficacy of LEA103—An experimental xylidide agent. Anaesthesiology 65:217, 1986.

Table 3. *Incidence of Ventricular Arrhythmias and Death After Intravenous Administration of Ropivacaine, Bupivacaine, and Lidocaine to Dogs**

	DOSE (MG/KG)	PEAK PLASMA CONCENTRATION (μG/ML)	ARRHYTHMIAS (NO. OF ANIMALS)	DEATHS (NO. OF ANIMALS)
Ropivacaine	9.8	68	2 of 6	1 of 6
Bupivacaine	8.6	67	5 of 6	5 of 6
Lidocaine	41.6	271	0 of 6	2 of 6

**Adapted from* Arthur GR, Feldman HS, Norway SB, et al: Acute IV toxicity of LEA-103, a new local anaesthetic, compared to lidocaine and bupivacaine in the awake dog. Anaesthesiology 65:182, 1986.

NEW PREPARATIONS

TOPICAL ANESTHESIA

Lidocaine is used extensively as a topical anesthetic, prepared in a liquid spray, cream, or gel. These preparations are only effective in penetrating mucosal membranes and are ineffective on intact skin. The development of an oil-in-water emulsion containing high concentrations of lidocaine and prilocaine in the base form resulted in EMLA, a cream that provides cutaneous local anesthesia.[7,51] Volunteer studies show that local anesthetic concentrations lower than 2.5 per cent are less effective in providing analgesia than 2.5 per cent and 5.0 per cent preparations.[22] The use of 5.0 per cent EMLA significantly reduced the pain of intravenous needle insertion, compared with the use of a placebo cream (Table 4), without producing any significant dermal irritation, even after repeated application. Furthermore, the potential for this preparation to produce toxic local anesthetic concentrations seems very low, with peak plasma drug concentrations occurring 180 minutes after application (75 ng per ml —lidocaine, 25 ng per ml—prilocaine). Several studies using EMLA in adults and children indicate a reduced degree of pain caused by

Table 4. *Percentage of Volunteers Experiencing Pain Associated with the Insertion of a 17-Gauge Needle Through the Skin of the Antecubital Area and the Dorsum of the Hand After the Application of Either Placebo Cream or 5% EMLA**

	ANTECUBITAL		DORSUM	
	Placebo	*EMLA*	*Placebo*	*EMLA*
No pain	8%	100%	0%	50%
Slight pain	58%	0%	50%	50%
Painful	33%	0%	50%	0%

**Adapted from* Evers H, Von Dordel O, Juhlin L, et al: Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA). Studies in volunteers. Br J Anaesth 57:997, 1985.

needle/cannula insertion.[19,21,27,28,41,44] One of the most appealing uses for this preparation is in the pediatric population in whom lessening their fear of needle insertion reduces stress on both the patient and physician. Its only drawback is the necessity of applying EMLA over the selected site for needle insertion 45 to 60 minutes prior to the procedure with an occlusive dressing. Shorter times of EMLA application result in a lower occurrence of pain alleviation. However, in one clinical study the timely application of EMLA was easily arranged in conjunction with administration of premedicant drugs.

EMLA was also investigated for the removal of skin grafts up to 0.53 mm in thickness.[52] Application area ranged from less than 50 cm^2 to over 1000 cm^2, and time of application ranged from 1.50 to 7.67 hours. Successful anesthesia was provided in 84 per cent of the cases, with the highest frequency of perception of moderate to severe pain occurring in those patients with application times exceeding 3 hours. Even after long application times over large surface areas, the highest plasma concentrations of lidocaine were 1.1 μg per ml and only 0.2 μg per ml for prilocaine. This indicates a wide margin of safety with regard to the possible occurrence of systemic toxicity.

REGIONAL ANESTHESIA

"Carbonation" or "Bicarbonation"?

Although carbonated local anesthetic solutions are not really "new" preparations (Bromage described their use in 1965[8]), a number of recent studies caused a resurgence of interest in this type of preparation. Bromage initially found that use of lidocaine carbonate for epidural anesthesia resulted in a more profound motor and sensory block and a more rapid onset than that seen with lidocaine hydrochloride. Current data on the use of these carbonated solutions are conflicting. For epidural anesthesia, carbonated lidocaine solutions were found to offer little or no advantage over lidocaine hydrochloride.[12,32,39,48] For example, in the study by Cole and co-workers, the solutions were administered epidurally for cesarean section and contained no epinephrine.[12] Drug solutions were given in aliquots at 3-minute intervals until either the total dose was administered or a sufficient level of anesthesia was obtained for surgery to proceed. Under these conditions, the onset, spread, and duration of block were very similar for both lidocaine preparations. The patients studied by Martin and co-workers received epidural lidocaine preparations as a bolus injection.[39] They concluded that carbonated lidocaine produced a more profound sensory block but otherwise found no other improvements in the blocks produced.

A similar pattern was seen with the use of the hydrochloride and carbonated forms of bupivacaine for epidural anesthesia. Two studies showed no statistical improvement in the speed of onset of action with the use of the carbonated solution,[43,64] whereas a study by Mattila and associates[40] found a more rapid onset and spread of sensory and motor blockade with the carbonated preparation. No great advantages were reported with the use of carbonated mepivacaine for either epidural[26] or axillary plexus block[20,38] nor with the use of carbonated lidocaine or carbonated bupivacaine for axillary brachial plexus block.[9,29] However, using epinephrine-containing solutions, Sukhani and Winnie[63] found carbonated lidocaine superior to lidocaine hydrochloride for brachial plexus block (Table 5).

The rationale behind the use of carbonated local anesthetics seems sound. Carbon dioxide should enhance the diffusion of local anesthetic through nerve membranes and thus produce a more rapid onset of block. This indeed was illustrated in isolated nerve preparations.[10,25] As carbon dioxide diffuses through the nerve membrane, the intracellular pH will be progressively reduced. This in turn will result in an increase in the intracellular concentration of charged (cationic) local anesthetic, which is the active form of the drug. Ion trapping will also occur, as the cationic form of the drug will not readily diffuse out of the cell. The result of these two events will be a more rapid onset and greater duration of conduction blockade. Why does this not consistently happen in a clinical setting? Because conflicting data exist in the literature, it would seem that clinical technique is important in the successful use of carbonated solutions. A single injection of a carbonated solution seems to produce a quicker onset of block. If the carbonated solution is not used rapidly after opening the vial, then much of the carbon dioxide will be lost into the atmosphere, thus reducing the efficacy of the preparation. It was also suggested that, owing to tissue buffering mechanisms, the intracellular pH is not decreased enough to produce an increase in the concentrations of cationic local anesthetic needed to cause a more rapid onset of block.[14]

A different approach involves the addition of sodium bicarbonate to the hydrochloride preparations immediately prior to their administration. With the increase in pH, the amount of drug existing as uncharged base is increased in solution. Because the uncharged form of local anesthetics most readily diffuses across cell membranes, the rate of local anesthetic penetration into the nerve will increase and a more rapid onset of block will occur. Clinical studies have so far con-

Table 5. *Onset and Duration of Sensory and Motor Anaesthesia After Brachial Plexus Block Using 1 Per Cent Lidocaine HCl and 1.1 Per Cent Lidocaine CO_2**

	SENSORY		MOTOR	
	HCl	*CO_2*	*HCl*	*CO_2*
Onset (minutes)—Proximal	7.3	4.3	4.1	2.7
—Distal	18.2	10.0	20.8	10.1
Duration (minutes)	235	230	240	245

**Adapted from* Sukhani R, Winnie AP: Clinical pharmacokinetics of carbonated lidocaine. I: Subclavian perivascular brachial block model. Anaesth Analg 66:739, 1987.

firmed these theories. DiFazio and co-workers[18] showed a more rapid onset of epidural analgesia (2 min) with lidocaine plus epinephrine and sodium bicarbonate (pH 7.20) compared with commercially available lidocaine plus epinephrine (5 min, pH 4.55). They also found a more rapid spread of analgesia at 5 to 15 minutes after injection with the pH-adjusted solutions. Similarly successful results were presented in other clinical papers for epidural[24] and brachial plexus block.[33]

This technique would initially appear more reliable than the use of carbonated solutions, but further clinical investigations need to be undertaken. This technique is not without its drawbacks. One of the reasons local anesthetics are prepared commercially as hydrochloride salts at acidic pH is to maintain them in solution. The base forms of the amide type local anesthetics are virtually insoluble in water and thus commercial solutions cannot be prepared at higher pH values. Moreover, the anesthesiologist must be careful not to increase the pH of commercial solutions too much since the local anesthetic will precipitate out of the solution as drug base. If this occurs, the problem is easily noticeable as the precipitating particles are readily visible to the naked eye.

COMBINATIONS AND ADDITIVES

A local anesthetic with a rapid onset of action but short duration and an agent of long duration but slow onset of action can be combined for regional anesthesia in an effort to utilize the best features of both drugs. The combination of chloroprocaine and bupivacaine should theoretically provide an ideal anesthetic solution producing a rapid onset and long duration of anesthesia. The initial reports by Cunningham and Kaplan[16] indeed suggested the usefulness of this combination. Later reports on epidural anesthesia[11] failed to confirm these findings. Although the combination of chloroprocaine and bupivacaine produced a rapid onset similar to chloroprocaine, the duration of anesthesia was significantly less than that resulting from bupivacaine alone. A metabolite of chloroprocaine may be responsible for the reduced duration of action of bupivacaine when this agent is combined with chloroprocaine.[13]

Mixtures of low doses of bupivacaine (12.5 mg) and fentanyl (150 μg)[65] or sufentanil (20 μg)[53] were successfully utilized for epidural analgesia during labor. Such combinations provided good analgesia while no motor blockade occurred, as was seen with the use of higher doses of bupivacaine. A reduction in bupivacaine dose provides greater safety in the event of an inadvertent intravenous or subarachnoid injection. In addition, the risk of hypotension associated with higher doses of epidural local anesthetics is reduced. The potential advantages of this type of combination of drugs remain to be fully elucidated.

The addition of potassium to lidocaine solutions potentiated infraorbital nerve blocks in a rat model[35] owing to the effect of potassium on the resting nerve membrane potential. In man, no beneficial effects were found when potassium was added to 0.5 per cent prilocaine solutions for intravenous regional anesthesia,[42] but when added to bupivacaine solutions for brachial plexus block, a faster onset of sensory blockade was observed.[60]

Both dextran and hyaluronic acid were added to local anesthetic solutions to prolong the duration of anesthesia. Although some degree of success was reported with the use of dextran,[6,50,57] the higher pH of the dextran solutions may be responsible for the prolonged blocks rather than the dextran itself.[58] Studies using infraorbital nerve blocks in rats indicated a prolonged duration of anesthesia with the use of hyaluronic acid,[30] but this was not the case with bupivacaine and prilocaine mixed with hyaluronic acid for ulnar nerve block in man.[34] As with the use of carbonated local anesthetic solutions, varying conclusions can be reached with regard to the various combinations of local anesthetics with other compounds, and again, further research needs to be undertaken in this area to fully elucidate the advantages and/or disadvantages of these mixtures.

NOVEL AGENTS

METHOXYFLURANE

Initial studies with a methoxyflurane preparation provided some interesting data regarding the potential for producing a long duration of local analgesia.[31,36] Lecithin-coated microdroplets of methoxyflurane, with a resulting concentration of 6.7 per cent (v/v) methoxyflurane with 2.7 per cent (w/v) lecithin, are prepared in an isotonic glucose solution. Although several other volatile agents were also tested in a similar formulation, only methoxyflurane produced a prolonged local anesthetic effect.[31] The model studied intradermal injections of the microdroplets into the rat tail. Using electric stimulation to elicit a pain response, this methoxyflurane formulation produced an elevated pain threshold for 25 hours, compared with only 3 hours for 0.5 per cent bupivacaine and 1.5 hours for 1 per cent lidocaine. The spread of anesthetic effect of methoxyflurane microdroplets was very small compared with conventional local anesthetics. Moreover, lidocaine and bupivacaine increased the pain threshold to a greater extent, although for a much shorter period of time. Limited studies in human volunteers indicate that this preparation is also effective when administered intradermally in man, with pain threshold returning toward control values over a 25-day period.[36] Although an anesthetic formulation of this type may not be useful for surgical anesthesia, it may be valuable for prolonged postoperative analgesia following local infiltration.

TETRODOTOXIN (TTX) AND SAXITOXIN (STX)

These biotoxins, which are derived from the puffer fish (TTX) and certain species of dinoflagellates (STX), specifically block sodium channels of nerve membranes when applied to their surface and thus produce conduction blockade. Studies of the local anesthetic properties of these compounds are limited. These compounds are approximately 250,000 times more potent than procaine for producing conduction blockade in isolated nerves.[15] However, both tetrodotoxin and saxitoxin are highly toxic. These agents will not readily pass through the epineurium surrounding peripheral nerves, and thus little or no conduction block was observed when they were used to perform sciatic nerve blocks in rats.[2] However, subarachnoid injection of tetrodotoxin in sheep will produce spinal anesthesia with a duration of almost 24 hours. When administered in conjunction with lidocaine for sciatic nerve block in the rat, the duration of anesthesia is significantly prolonged.

Other problems associated with saxitoxin and tetrodotoxin include their complex structure, which makes them difficult to synthesize, and their instability in aqueous solutions. If the active part of the molecule were identified and incorporated into a more chemically stable compound, the potential exists for producing a clinically useful local anesthetic with a very long duration of action.

QUATERNARY AMINES

Although quaternary amine compounds will produce conduction blockade of long duration when applied internally into a nerve, these compounds are unable to penetrate the nerve membrane and thus appear to be of little value as clinically useful drugs. Ross and Akerman[59] reported data relating to tertiary amine compounds capable of penetrating nerve membrane that will undergo a cyclization reaction to produce quaternary amines. The major problem with this group of compounds is the formation of the quaternary amine prior to penetration of the nerve membrane. If this cyclization could be reliably controlled so the reaction did not occur until the tertiary amine penetrated the nerve membrane, then a clinically useful long-acting local anesthetic may possibly be developed.

POTASSIUM CHANNEL BLOCKERS

Unlike the currently useful local anesthetics that affect the membrane sodium channels and thus inhibit the depolarization of the nerve action potential, potassium channel blockers inhibit the repolarization of the nerve action potential. Tetraethylammonium (TEA) is such a compound. The synthesis of several TEA derivatives based on the lengthening of an alkyl side chain produced a series of compounds capable of producing anesthesia for infraorbital nerve block in a rat model for periods ranging from 1 hour to 20 days.[17,62] The carbon chain length was varied from C_2 to C_{16}, and a maximal effect was obtained at a carbon chain length of C_{12}. In this model, blocks were fully reversible and no signs of neurotoxicity were observed. Application of these compounds for intrathecal blocks (C_{12} derivative) resulted in profound neurotoxicity that resulted in paralysis due to spinal cord degeneration. Although these data are somewhat discouraging, production of series of chemically similar compounds may result in an agent that is not neurotoxic but is still capable of blocking potassium channels and producing the desired local anesthetic effect.

SUMMARY

Although no new local anesthetic agents were introduced into clinical practice during the past 10 years, a number of developments occurred in recent years with regard to agents for regional anesthesia. In terms of conventional local anesthetic drugs, ropivacaine represents a new amino-amide type of agent that has been extensively studied in laboratory animals. The results to date suggest that ropivacine may be capable of providing a prolonged duration of anesthesia, similar to bupivacaine, but with an improved margin of safety in terms of cardiovascular toxicity.

In the field of topical analgesia, EMLA has already been studied extensively in clinical situations. This preparation, which consists of a eutectic mixture of lidocaine and prilocaine, may be the first useful means of providing effective topical cutaneous analgesia and should be of particular value in pediatric patients.

Several novel types of local anesthetic preparations are currently being investigated. In this regard, the microdroplet formulation of methoxyflurane appears to provide prolonged periods of analgesia following local infiltration.

The use of combinations of local anesthetics and opiates for prolonged analgesia also is an area of increasing interest. Low concentrations of local anesthetics with an opiate such as fentanyl are currently useful for continuous epidural analgesia during labor. In addition, such combinations are also valuable for prolonged postoperative pain relief.

Carbonated solutions of local anesthetics, or the use of pH-adjusted solutions by the addition of bicarbonate, appear useful to reduce the onset time of conduction blockade, particularly when employed for brachial plexus anesthesia.

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What's New in Cardiac Drugs?

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The growing sophistication in medical management of serious disease states and the expansion of aggressive surgical techniques that encompasses this added volume of complex conditions have presented an increasing challenge to the anesthesiologist and intensive care specialist. Optimizing such patients' conditions during a perioperative period requires first that one develop a clear understanding of the fine details of the physiologic characteristics that define the illness. Then one must choose a management plan that will most effectively normalize those derangements without creating other abnormalities. In the case of the cardiovascular system, this often means intervening pharmacologically. Many vasoactive compounds exist that will successfully accomplish the intended goal, yet there have been gaps in the spectrum of desirable effects of cardiovascular drugs. In this chapter, three new cardiac drugs will be discussed that partially fill this void. Each has one or more distinctive characteristics that provide the clinician with a better opportunity to optimally manage complex cardiovascular problems.

A NEW INOTROPIC DRUG

Congestive heart failure (CHF) is a prevalent disease, affecting some 3 million people in the United States alone.[20] Pharmacologic treatment for this condition dates to over 200 years ago with the introduction of digitalis. The fact that digitalis, which is plagued by low potency and a narrow therapeutic/toxic margin, is still widely used for the treatment of congestive heart failure illustrates the need for new pharmacologic therapy. While the administration of catecholamines is effective in the acute management of critical congestive

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heart failure, long-term treatment with this class of cardiotonic agents is impractical, as tolerance to their inotropic actions occurs. Diuretics and vasodilators are efficacious in most cases and can be given chronically by mouth. However, these drugs only ameliorate the secondary effects of congestive heart failure—fluid retention and increased afterload—and do not act on its primary cause—insufficient myocardial contractility.

This predicament, in conjunction with the progress made in our understanding of the cellular mechanisms of myocardial activation and the contractile state, led to the recent development of new agents for more definitive therapy of congestive heart failure. The first of these approved for use, amrinone, was initially developed in both intravenous and oral formulations, with the hope that chronic oral therapy might provide a solution to this dilemma. While this particular goal was not reached, investigations using its intravenous formulation in the acute management of congestive heart failure demonstrated that the drug may be useful for the anesthesiologist and intensivist to treat the failing heart.

AMRINONE

Amrinone (Inocor, Sterling-Winthrop), a bipyridine derivative, was first synthesized in 1977 and found to possess cardiac stimulant and vasoactive properties.[5] FDA approval for use in the United States was obtained in 1984, making amrinone available for parenteral use in the treatment of congestive heart failure. The chemical formula for amrinone is 5-amino-3,4′-bipyridin-6(1H)-one, and the drug is synthesized as a complex with lactic acid (Fig. 1). It is a pale yellow compound dissolved in sterile water and buffered to a pH of 3.2 to 4.0 to provide adequate solubility at a concentration of 5 mg per ml. Sodium metabisulfite is present as a preservative. The ampules should be protected from light and can be stored at room temperature. The drug should not be diluted for infusion in glucose-containing solutions, as this will result in loss of 11 to 13 per cent of the agent's activity over 24 hours.[164] However, amrinone can be infused

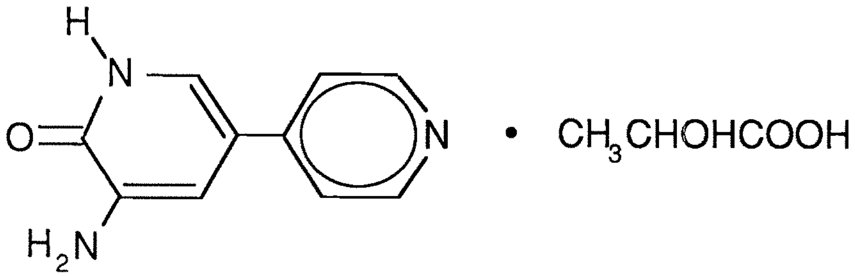

Figure 1. Chemical structure of amrinone.

in a running glucose line. Furosemide injected into an intravenous line containing amrinone will form a precipitate.

Metabolism and Pharmacokinetics

The pharmacokinetics of intravenously administered amrinone in healthy volunteers fit a two-compartment open model of distribution and elimination.[128] The apparent volume of distribution is 1.2 L per kg and protein binding is variable from 10 to 50 per cent.

The drug rapidly redistributes with a distribution half life of 4.6 minutes. The terminal elimination half-life is 3.6 hours. However, in patients with severe congestive heart failure, elimination is prolonged (half-life of about 5.8 hours).[42] This is an important consideration, since it is this group of patients in which amrinone finds its greatest use.

Amrinone undergoes several hepatic biotransformation steps, including acetylation and conjugation with glutathione and glucuronide. However, the primary route of elimination is renal, with up to 80 per cent of administered amrinone being excreted in the urine, half of this in its unchanged form.[164] None of the metabolites has been reported to have pharmacologic activity.

Mechanism of Action

The inotropic capacity of the myocardial cell is directly proportional to the amount and duration of increase in intracellular calcium concentration [Ca^{++}] during a contraction.[147] Thus, a common mode of action of all cardiotonic drugs is to enhance [Ca^{++}]. Different classes of inotropic drugs accomplish this via various mechanisms. Cardiac glycosides act to increase [Ca^{++}] by inhibiting the sodium-potassium adenosine triphosphatase (NaK-ATPase) present on the cell membrane. This causes an increase in intracellular Na^+, which limits transmembrane Na^+-Ca^{++} exchange and results in a secondary rise in [Ca^{++}]. Catecholamines stimulate cardiac adrenergic receptors, resulting in increased production of intramyocardial cyclic adenosine monophosphate (cAMP). CAMP, by activating various protein kinases, acts both to facilitate Ca^{++} entry into the cytosol and to enhance its transport within the cell.[134]

Amrinone increases cAMP by inhibiting a phosphodiesterase isoenzyme (PDE III), which catalyzes its hydrolysis. PDE III is present as a particulate subunit attached to the sarcolemmal membrane. The inhibitory activity appears specific for PDE III, which sets amrinone apart from the methyl xanthines and caffeine, which inhibit all PDE isoenzymes. A secondary mechanism of amrinone's inotropic action may be an interference with the Na^+-Ca^{++} exchange mechanism,[52] although it was shown that amrinone does not share with digitalis an inhibitory effect on NaK-ATPase.[6] In addition, in high doses amrinone may enhance the sensitivity of myofibrillar ATPase to Ca^{++}, amplifying the response of the myocardial contractile elements in the final pathway of activation.[48,147]

An important effect of amrinone that is mainly responsible for its overall hemodynamic profile is peripheral vasodilation. Similar to the mechanism in myocardial cells, this effect is mediated in vascular smooth muscle through an inhibition of PDE III with subsequent increased cAMP. In these cells this results in decreased calcium uptake and vascular relaxation.[101,124] This appears to be a direct effect, with no dependence on reflexive response to other hemodynamic actions.[99] In preparations of isolated myocardium and vascular smooth muscle, amrinone displayed a vasodilator potency 10 to 100 times greater than that of its inotropic capacity.[123] The postulated mechanisms of action of amrinone are summarized in Figure 2.

Hemodynamic Effects

The combination of profound peripheral vasodilation and increased myocardial contractility via a novel intracellular pathway places amrinone in a unique category of cardiotonic agents. In many clinical studies examining the hemodynamic effects of the drug,

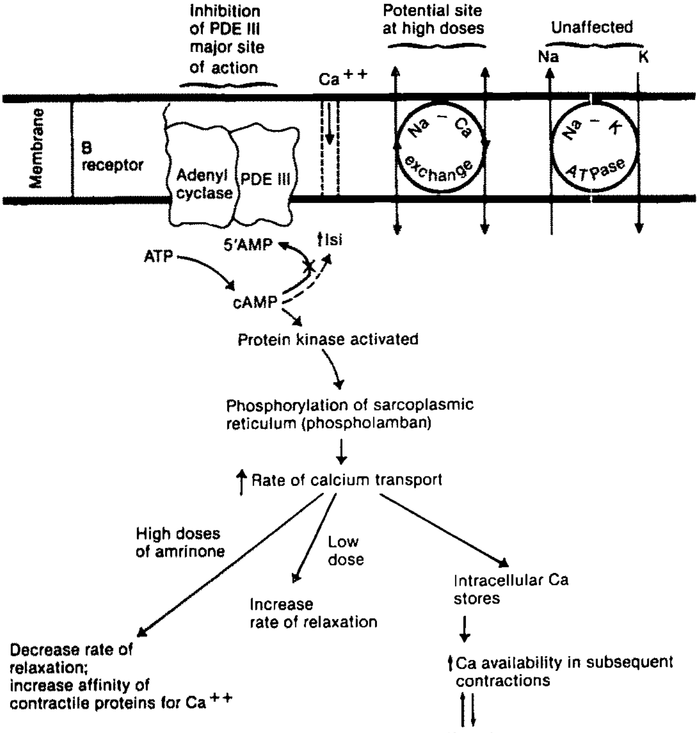
Inhibition of PDE III major site of action
Potential site at high doses
Unaffected
Na
K
Ca++
Membrane
B receptor
Adenyl cyclase
PDE III
Na – Ca exchange
Na – K ATPase
ATP
5'AMP
↑Isi
cAMP
Protein kinase activated
Phosphorylation of sarcoplasmic reticulum (phospholamban)
↑Rate of calcium transport
High doses of amrinone
Low dose
Increase rate of relaxation
Intracellular Ca stores
Decrease rate of relaxation; increase affinity of contractile proteins for Ca++
↑Ca availability in subsequent contractions
↑Tension

Figure 2. Postulated mechanism of action of amrinone. Ca = calcium; ↑ = increase; ↓ = decrease; ISi = slow inward calcium current; PDE = phosphodiesterase; X denotes inhibition. (*From* Mancini D, LeJemtel T, Sonnenblick E: Intravenous use of amrinone for the failing heart. Am J Cardiol 56:8B, 1985; with permission.)

amrinone was consistently found to increase cardiac index and to decrease both systemic and pulmonary vascular resistance while leaving heart rate and mean systemic arterial pressure generally unchanged (Table 1). The degree of improvement in cardiac performance is proportional to the plasma level of amrinone, with analysis suggesting that a concentration of 4 μg per ml yields a 50 per cent increase in cardiac output.[41]

The decrease in wall tension caused by the lowered preload and afterload and the unaltered heart rate allow the augmented contractility to be tolerated with no change or a decrease in overall myocardial oxygen consumption (MVO_2).[84] This finding has important implications for patients with ischemic heart disease and congestive cardiac failure. In this population, parenteral amrinone decreased myocardial lactate extraction and myocardial oxygen consumption despite a near doubling of cardiac index.[15] No patient in this study experienced an exacerbation of their angina. These beneficial effects may not apply to all cases of myocardial ischemia, however. Hartog and co-workers[73] studied the effects of amrinone in a porcine model of myocardial ischemia. The drug caused an improvement in function but not overall perfusion of the ischemic area, and only for a short period of time (10 min) despite continued high doses (1 mg per kg bolus followed by 50 μg per kg per min infusion). Moreover, there were significant drops in mean arterial pressure, left ventricular filling pressure, and cardiac output with amrinone administration, suggesting that the primary effect of the drug was profound vasodilation. In this study, data were obtained for a period of only 25 minutes after starting amrinone. One might speculate that protracted exposure to such hemodynamic conditions in the clinical setting of acute ischemia in a non-failing ventricle would eventually lead to exacerbation rather than relief of the ischemia. In another study, Rude and colleagues[146] demonstrated in a similar model in dogs that amrinone

Table 1. *Hemodynamic Effects of Amrinone**

REFERENCE	AMRINONE DOSE	PATIENTS (n)	MEAN CHANGE FROM BASELINE (%)						
			CI†	PCWP	RA	SVR	PVR	SAP	HR
Siskind et al[153]	40 μg/kg/min	8	+37	−17	−49	−23	—	NS	NS
Klein et al[94]	40 μg/kg/min	8	+46	−25	−37	−19	—	NS	NS
LeJemtel et al[104]	0.75–3 mg/kg	8	+49	−26	−26	−29	−39	NS	NS
Benotti et al[14]	0.5–3.5 mg/kg	8	+44	−46	−33	−32	−24	NS	NS
Benotti et al[15]	2.5 mg/kg	9	+69	−16	−18	−40	−50	NS	NS
Weber et al[169]	1.5–3.5 mg/kg	11	+47	−41	—	—	—	NS	NS
Naccarelli et al[125]	10–20 μg/kg/min‡	14	+30	−20	−21	−17	−8	NS	NS
Total			+45	−27	−29	−26	−27	NS	NS
n			66	66	55	55	55	66	66

**Adapted from* Goldstein R: Clinical effects of intravenous amrinone in patients with congestive heart failure. Circulation 73 (Suppl III): 191, 1986; with permission

†CI = cardiac index; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; SAP = mean systemic arterial pressure; HR = heart rate.

‡Infusion started after loading dose of 1.5 mg/kg.

caused an augmentation in ST segment elevation of epicardial electrograms and in intramyocardial CO_2 production. Thus, the particularly favorable influence of amrinone over other inotropes in myocardial ischemia is probably limited to those patients in whom the imbalance in myocardial energetics is primarily due to dilated cardiomyopathy with increased wall tension instead of pure coronary artery insufficiency.

The synthetic catecholamine dobutamine, which has predominantly β receptor agonist properties, has been used clinically to elicit similar hemodynamic effects. While comparative studies of these drugs for the treatment of congestive heart failure demonstrate a similar improvement in cardiac index and reduction of pulmonary capillary wedge pressure,[94] dobutamine does so at the expense of a substantial increase in myocardial oxygen consumption.[13] In another comparative study, the inotrope dopamine caused unacceptable increases in heart rate and a far smaller decrease in left ventricular filling pressures than either amrinone or dobutamine.[16]

Sustained administration of catecholamines may be associated with tachyphylaxis or decreased pharmacodynamic response despite sustained tissue drug level. This is probably due to a down regulation[22,23] or desensitization[71] of β receptors in congestive heart failure. Amrinone, being independent of this pathway, does not cause this phenomenon and has been found to maintain its effect for protracted periods.[112]

Investigators studied the efficacy of combining catecholamines and amrinone in the treatment of severe congestive heart failure. Amrinone provided additional improvement in indices of cardiac performance when used as a supplement to dobutamine therapy compared with the effects of dobutamine alone.[53] In the growing population of patients with end-stage heart disease who are awaiting cardiac transplantation, this combination can offer a critically needed extension of the period of cardiac stability.[69] In studies of patients with moderate to severe cardiac failure following cardiac surgery, who were already being treated with substantial doses of adrenergic agents, the addition of amrinone provided marked improvements in overall cardiac performance.[56,144]

Other studies have examined the afterload reducing properties of amrinone in comparison to other vasodilators. Amrinone decreased systemic vascular resistance and increased cardiac output to a similar degree as hydralazine, and acted synergistically when these two drugs were combined.[151] Amrinone and sodium nitroprusside both elevated cardiac output and reduced left ventricular end diastolic pressure and aortocoronary sinus oxygen difference.[170] However, systemic blood pressure and maximum rate of pressure development (dP/dt) were decreased only by nitroprusside. Konstam and colleagues[99] confirmed the significance of the positive inotropism of amrinone by demonstrating that amrinone increased cardiac index more than did an equal afterload reduction by nitroprusside.

In a study of patients with idiopathic pulmonary hypertension, amrinone decreased pulmonary vascular resistance commensurate with an increase in cardiac output. However, amrinone did not decrease pulmonary artery pressure.[139] In a somewhat different group of patients, those in whom pulmonary hypertension was caused by chronic mitral stenosis, amrinone caused a slight but significant drop in mean pulmonary artery pressure.[74] Table 2 describes the hemodynamic profile of a patient recently undergoing aortic valve replacement at our institution. This patient had developed congestive heart failure and severe pulmonary hypertension as a result of aortic insufficiency. Amrinone, given as a 2 mg per kg bolus and 10 μg per kg per min continuous infusion, was used as the primary inotropic agent to support weaning from cardiopulmonary bypass. A low dose of epinephrine (0.03 μg per kg per min) was also used. Pulmonary artery pressure and vascular resistance were reduced by more than 50 per cent, and cardiac output was substantially improved using this inotropic regimen, making perioperative management straightforward and uncomplicated. Clearly, amrinone has great utility in settings such as this.

Electrophysiologic Effects

In investigations using isolated Purkinje fibers amrinone exerted no significant influence on most action potential parameters, such as resting membrane potential, action potential amplitude or duration, maximum upstroke, or conduction velocity.[98,126,130] Goldstein and associates[59] reported the results of electrophysiologic studies of 15 patients with advanced congestive heart failure treated with intravenous amrinone. They found a modest decrease in atrial and AV nodal refractory periods and a slight increase in maximal AV conduction, suggesting that amrinone may cause an enhanced response to supraventricular tachydysrhythmias. In the same study, patients placed on oral amrinone were Holter monitored for 1 to 2 days and found to have no increase in the frequency of PVCs or episodes of ventricular tachycardia, although there was a trend toward an increase in ven-

Table 2. *Use of Amrinone in a Patient with Severe Aortic Insufficiency and Pulmonary Hypertension Undergoing Aortic Valve Replacement**

	PRE-CPB	POST-CPB
Heart rate	75	95
Systemic blood pressure	110/70	105/50
Pulmonary artery pressure	105/55	42/20
Pulmonary capillary wedge pressure	30	10
Pulmonary vascular resistance (Woods units)	10.8	4.1
Cardiac output	2.8	4.5

*Pre-CPB = period following institution of general anesthesia with midazolam, sufentanil, and isoflurane, prior to cardiopulmonary bypass; Post-CPB = period immediately following weaning from cardiopulmonary bypass (aortic cross clamp time: 2 hours) using amrinone (2 mg/kg bolus, 10 μg/kg/min) and epinephrine (0.03 μg/kg/min) as inotropic support.

tricular couplets. However, in clinical trials, dysrhythmia was a cited side effect in 3 per cent of cases.[164]

Interactions with Anesthetics

The hemodynamic effects of amrinone have been studied during general anesthesia in experimental preparations. Boncyk and coworkers[18] reported that amrinone in high doses could overcome the myocardial depressive effects of high concentrations of halothane, but in so doing caused significant decreases in blood pressure compared with dobutamine. In a similar study, Makela and Kapur[111] demonstrated that amrinone could reverse the decrease in cardiac index and prevent the increases in systemic and pulmonary vascular resistance caused by 2.2 to 2.4 per cent end-tidal enflurane without causing significant change in mean arterial pressure from baseline measurements. Thus, it was suggested that amrinone may provide a useful means of improving cardiac performance in the presence of potent inhalational anesthetics.

Adverse Effects and Complications

Amrinone has many untoward side effects.[51] They were most apparent during the testing of orally administered amrinone and include intractable abdominal pain, nausea, headache, dizziness, thrombocytopenia, dysrhythmia, fever, and abnormalities of hepatic function tests.[39] These reactions prompted the withdrawal of treatment in 34 to 72 per cent of patients in various trials.[39,127,152] Moreover, careful examination of cardiac performance with long-term use[172] and controlled placebo trials[39,114] indicated that oral amrinone lacked efficacy. For this reason and because an analogous compound milrinone, which reportedly lacks many of the side effects, is under investigation, the oral formulation of amrinone was withdrawn. The incidence of side effects in short-term intravenous use is far less frequent than with oral administration[164] (Table 3).

Amrinone-induced thrombocytopenia has been studied specifically. The likely cause is an accelerated peripheral loss of platelets via a non-immunologic mechanism with no indication of suppression of production.[9] Other studies indicated that the platelet loss is directly proportional to the plasma concentration of amrinone and may occur more frequently if high doses are maintained for extended periods.[171] In a recent small study of acute use, amrinone did not alter platelet count.[75] In no patient has hemorrhage been attributable to thrombocytopenia.

Dosage

The dose of amrinone recommended by the manufacturer is 0.75 mg per kg given as a bolus over 2 to 3 minutes followed by an infusion of 5 to 10 μg per kg per minute. However, in many clinical

Table 3. *Adverse Reaction Profile from Clinical Studies with Intravenous Amrinone in 462 Patients**

ADVERSE REACTION	INCIDENCE (%)
Arrhythmia	3.0
Thrombocytopenia	2.4
Gastrointestinal	
Nausea	1.7
Vomiting	0.9
Abdominal pain	0.4
Anorexia	0.4
Hypotension	1.3
Fever	0.9
Liver enzyme alterations	0.2
Chest pain	0.2
Burning at the site of injection	0.2

**From* Treadway G: Clinical safety of intravenous amrinone—a review. Am J Cardiol 56:39B, 1985; with permission

studies, the bolus doses were higher (1.5 to 2.5 mg per kg), or patients were given second boluses of the drug within 20 to 30 minutes of the first with no untoward effect.[16,53,104,144]

Summary

Although amrinone did not meet early expectations as an effective drug in the chronic treatment of congestive heart failure, the intravenous formulation is very useful in the acute treatment of severe cardiac decompensation. For the anesthesiologist faced with managing a patient with dilated cardiomyopathy, especially if high doses of adrenergic agents are already in use, amrinone can be a highly beneficial drug in providing cardiac support and stability. Amrinone should be considered in any patient with heart failure and high systemic vascular resistance.

NEW ADRENERGIC ANTAGONISTS

There are at least two α adrenergic receptors as well as two β adrenergic receptors distributed in various tissues. Table 4 lists the various receptor types, sites, and physiologic responses to both α and β adrenergic stimulation. α_1 adrenoceptors are located postsynaptically on vascular smooth muscle and mediate the vasoconstrictive response to norepinephrine, which is the neurotransmitter of the postganglionic sympathetic fibers. The α_2 subtype is usually located presynaptically on these fibers, and when stimulated, exerts a negative feedback inhibition of norepinephrine release.[76] However, the predominant effects of the new adrenergic antagonists discussed are at the β receptors.

Table 4. *Physiologic Adrenoceptor Effects*

TISSUE OR ORGAN	RECEPTOR TYPE STIMULATED	PHYSIOLOGIC RESPONSE
Heart	beta_1 (beta_2)†	Increased rate Increased force of contraction Increased conduction
	(alpha_1)	Increased force of contraction
Arteries	alpha	Vasoconstriction
	beta_2	Vasodilatation
Veins	alpha	Vasoconstriction
Bronchial smooth muscle	beta_2 (beta_1)	Bronchodilatation relaxation
Liver	beta_2	Glycogenolysis, gluconeogenesis
Skeletal muscle	beta_2	Glycogenolysis, lactate production
Pancreas	alpha	Decreased insulin secretion
	beta_2	Increased insulin and glucagon release
Kidney	beta_1 (beta_2)	Renin release

†Parenthesis denotes minor effect

β blocking drugs competitively antagonize the β adrenergic receptor, and may possess the following pharmacologic characteristics: cardioselectivity (exclusive β_1 antagonism as opposed to combined β_1/β_2 antagonism), intrinsic sympathetic activity (ISA), and membrane stabilization. The various β blockers can then be categorized according to these effects (Table 5).

The advantages of cardioselective β blockers are that they are less likely to produce bronchial smooth muscle constriction or increase systemic vascular resistance. However, there are no significant differences in the heart rate and blood pressure responses to operative stress (intubation, incision, etc.) in patients treated with cardioselective versus non-cardioselective β blockers.[36] Intrinsic sympathetic activity refers to partial β agonist properties of some of the β blockers (e.g., pindolol, oxprenolol, practolol, and acebutolol). In general, intrinsic sympathetic activity drugs produce less reduction in heart rate and cardiac output than do drugs that lack this property.

The useful clinical effects of β adrenoceptor blocking drugs are listed in Table 5. All reduce heart rate, contractility, and conduction and there are only subtle differences based on the cardioselectivity and intrinsic sympathetic activity effects. It is important to realize that the effects of β blockers are primarily dependent on two factors: (1) the degree of sympathetic tone and (2) the β receptor responsiveness (related to the number and sensitivity of β receptors). For ex-

Table 5. *Associated Pharmacologic Properties of the Beta-Blocking Drugs**

Drug	Relative Beta$_1$ Selectivity	Intrinsic Sympathomimetic Activity	Membrane-Stabilizing Activity
Acebutolol	+	+ +	+
Atenolol	+ +	0	0
Esmolol	+ +	+	+
Labetalol†	0	? + B_2	+
Metoprolol	+ +	0	0
Nadolol	0	0	0
Pindolol	0	+ +	0
Propranolol	0	0	+ +
Timolol	0	0	0

**From* Kates RA: Antianginal drug therapy. *In* Kaplan JA (ed): Cardiac Anesthesia, 2nd ed. Philadelphia, PA, Grune & Stratton, 1987, P 451; with permission.

†Labetolol has additional alpha-adrenergic blocking activity.

ample, β_1 receptor responsiveness decreases with age[50] and in congestive heart failure.[24]

ESMOLOL

Most β blockers are relatively long-lived compounds as reflected by their elimination half-lives (Table 6). In 1982, Zaroslinski and co-workers[174] envisioned a β blocker rapidly metabolized to inactive by-products similar to catecholamines. Esmolol (ASL-8052, Brevibloc, American Critical Care), a phenoxypropanolamine, was the product of this concept and was synthesized in 1982[43,44] (Fig. 3). It contains an ester in the paraposition of the phenyl ring. The presence and location of this ester determine esmolol's cardioselectivity as well as its ultrashort duration of action.[43] Esmolol is unique among β blockers because of its extremely rapid onset and metabolism.

Table 6. *Beta-Adrenergic Antagonists*

	t_{12} Elimination	Route
Atenolol	6–9 h	PO
Metoprolol	3–4 h	PO, IV*
Nadolol	17–24 h	PO
Pindolol	3–4 h	PO
Propranolol	4–6 h	PO, IV*
Timolol	4–5 h	PO
Esmolol	9 min*	IV*

*Distinctive characteristic

PO = oral; IV = intravenous

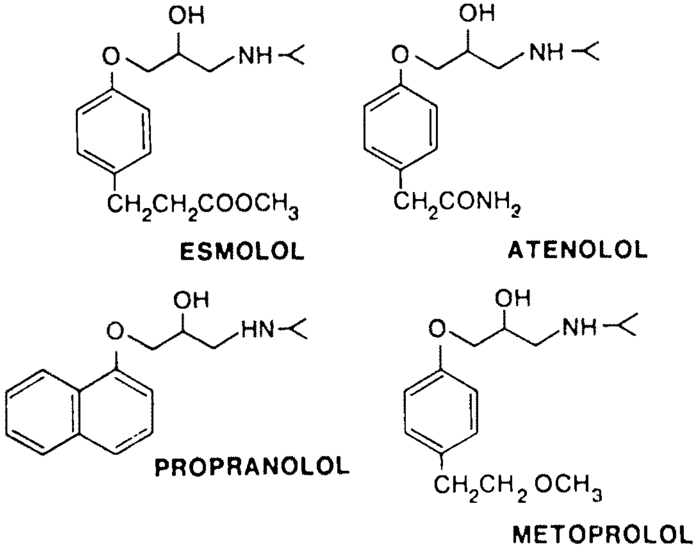

Figure 3. Chemical structure of common β adrenergic antagonists.

Physicochemical Characteristics

Esmolol hydrochloride is a white, odorless, crystalline compound[8] that is highly water soluble. It is formulated in solutions of 100 mg per ml esmolol hydrochloride, 10 per cent alcohol, and propylene glycol in water and will also be available in a 250 mg per ml solution.[8] An additional formulation of 10 mg per ml esmolol for bolus administration is planned. Solutions of esmolol are somewhat acidic and are buffered with acetate to a pH of 4.9 to 5.1. Esmolol must be diluted for use as a continuous infusion, usually to a final concentration of 10 mg per ml in normal saline. The formulated solutions are stable for months at room temperature, and the 10 mg per ml dilutions are stable for at least 24 hours at room temperature or when refrigerated.[8]

Metabolism and Pharmacokinetics

The major pathway of esmolol metabolism is hydrolysis of the methyl ester, which produces methanol and ASL-8123 (3-[4-2-hydroxy-3-isopropylamino propoxyphenyl] propionic acid), which is excreted renally.[155] Although methanol can be a toxic metabolite, its predicted plasma concentrations after infusion of esmolol are 50 to 100 times less than those associated with toxicity (data on file, American Critical Care). ASL-8123 is a longer acting metabolite but is about 1000-fold less potent than esmolol as a β blocker.[61] The β blocking effects of esmolol are dissipated when the metabolite is at peak blood levels, showing no effect of the metabolite.[155]

The cytosol esterases of the red blood cell appear to be the primary site of esmolol hydrolysis. Thus, patients with atypical or deficient plasma cholinesterase should not experience a prolongation of esmolol's effect. It has been shown that esmolol and ASL-8123 can inhibit plasma cholinesterase, but *in vitro* studies have proven this to be unlikely.[11] Thus, esmolol should not inhibit the metabolism of succinylcholine.

Esmolol is very efficiently cleared from the blood. Only about 1 per cent is excreted unchanged in the urine.[1,155] The pharmacokinetic variables for esmolol in normal volunteers and patients having coronary artery bypass surgery are listed in Table 7.[37] Of note is the elimination half-life of approximately 10 minutes. This is distinctly shorter than any of the other available β blockers. Moreover, esmolol's volume of distribution is large, indicating extensive distribution to the tissues. The metabolite ASL-8123 is more slowly cleared, primarily via unchanged excretion in the urine. Its elimination half-life is about 4 hours.[155]

The fact that esmolol is rapidly eliminated has pharmacodynamic significance, since there is an excellent correlation between the blood level of esmolol and its antagonism of the heart rate and blood pressure effects of isoproterenol.[155] Sum and co-workers[155] reported a correlation between the average changes in the ratio of heart rate or systolic blood pressure and the logarithm of the esmolol blood concentration. There was a very poor association of the blood metabolite level and hemodynamic changes, suggesting that the metabolite has virtually no effect.

Mechanism of Action

The biochemical basis of esmolol's actions has not been reported but is assumed to be similar to that of other β blocking drugs. β receptors are located on the surface of cell membranes, and when stimulated (by catecholamines or dopamine, as well as other synthetic drugs) activate intracellular adenyl cyclase, which catalyzes the formation of cyclic 3′5′-adenosine monophosphate (cAMP) from adenosine triphosphate. CAMP catalyzes the activation of intracellular kinases, which produce the β adrenergic effects of the cell. A β adrenergic blocking drug prevents the effect of the agonist. The bio-

Table 7. *Comparison of Esmolol Pharmacokinetic Parameters**

	DURING ANESTHESIA		VOLUNTEERS	
	Mean ± SD	*COV (%)*	*Mean ± SD*	*COV (%)*
α (min^{-1})	0.749 ± 0.601	82.2	0.364 ± 0.095	NA
$t_{1/2}\alpha$ (min)	1.34 ± 0.77	57.8	2.030 ± 0.544	NA
$t_{1/2}\beta$ (min)	9.9 ± 4.55	46.4	9.190 ± 3.510	38
CI ($ml \cdot kg^{-1} \cdot min^{-1}$)	128 ± 41	31.9	285 ± 104	36.5
$V\beta$ ($L \cdot kg^{-1}$)	1.90 ± 1.24	65.2	3.430 ± 1.420	41.4

**From* de Bruijn N, Reves J, Croughwell N, et al: Pharmacokinetics of esmolol in anesthetized patients receiving chronic beta blocker therapy. Anesthesiology 66:323, 1987; with permission

NA = not available; COV = coefficient of variation chemical mechanism of receptor sensitivity has not been established. However, it is known that cardioselective drugs such as esmolol have a far greater affinity for β_1 receptors than for β_2 receptors.[156]

Esmolol has been studied *in vitro* using guinea pig atria and tracheal tissues. In these models, esmolol caused a concentration-dependent rightward parallel shift in the isoproterenol concentration-response curve in atria and, at a higher concentration, in trachea, indicating a competitive blockade of β-adrenergic receptors. Esmolol possesses a small degree of intrinsic sympathetic action as shown in isolated guinea pig atria[64] and like many other β blockers has a weak local anesthetic action at extremely high concentrations.

The onset of action of esmolol is rapid. β blockade effects reach steady state as early as 10 minutes following initiation of infusion. The time to recovery from blockade is also very rapid. The times to 50 per cent and 80 per cent recovery after infusion varied from 4 ± 1 to 17 ± 1 minutes[64] and indicated that recovery time is somewhat dependent on previous infusion rate. Intravenous infusions of esmolol in vagotomized dogs reduce baseline heart rate and result in dose-dependent blockade of isoproterenol-induced tachycardia but have no effect on the isoproterenol-induced decrease in diastolic blood pressure. This is in clear contrast with results obtained with propranolol, which blocks both the heart rate and blood pressure responses, reflecting the cardioselective action of esmolol.[64] Intravenous infusions of esmolol do not alter perfusion pressure in sympathetic ganglion–blocked dogs, which suggests that it has no direct effect on vascular smooth muscle. Esmolol does not produce α blockade and has no vasodilating properties.[64]

Hemodynamic Effects

A preload recruitable stroke work area (PRSWA) model in chronically instrumented awake dogs was used to evaluate the effects of esmolol on myocardial contractility. Large doses of esmolol impaired left ventricular function without reducing heart rate, suggesting a direct negative inotropic effect.[82] The effects of esmolol on cardiac hemodynamics, coronary artery blood flow, and myocardial oxygen consumption in other studies are typical of β blockers in general. Esmolol produces significant dose-dependent decreases in heart rate, right and left ventricular contractility, and diastolic arterial blood pressure in barbiturate-anesthetized dogs.[63] Esmolol reduces myocardial oxygen consumption by decreasing heart rate and contractility[62] (Fig. 4).

The hemodynamic effects of esmolol and propranolol were compared using radionuclide angiography in a double-blind randomized crossover study in 15 patients at rest and during peak upright exercise. At rest, both drugs significantly decreased heart rate, systolic blood pressure, left and right ventricular ejection fractions, and cardiac index. Exercise caused the same hemodynamic changes except that left ventricular ejection fraction was not decreased (Fig. 5). The

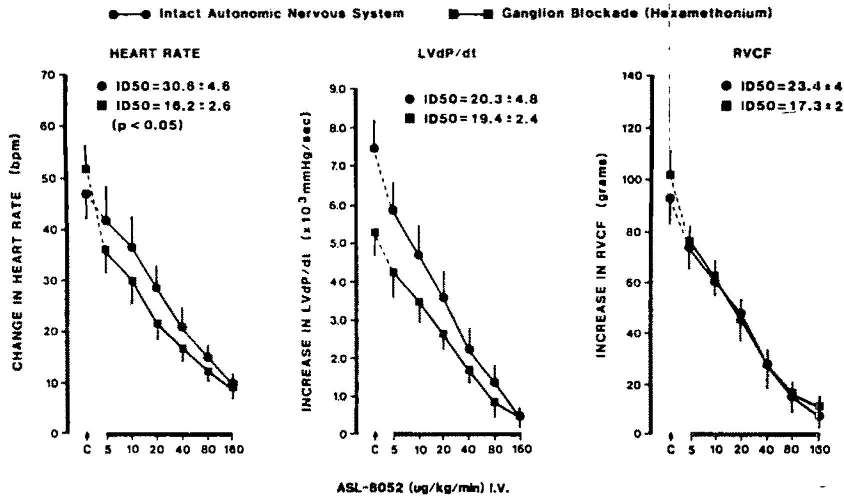

Figure 4. Esmolol effect on heart rate, left ventricular dP/dt, and right ventricular contractile force responses to isoproterenol in the presence and absence of ganglion blockade. ID50 values = dose rate (μg/kg/min) esmolol associated with 50 per cent decrease in control responses. (*From* Gorczynski R, Murthy V, Hwang T: β-blocking and hemodynamic effects of ASL–8052. J Cardiovasc Pharmacol 6:1048, 1984; with permission.)

systolic blood pressure was lower in the esmolol group during exercise, which was the only significant difference between the two groups.[80] Other clinical studies demonstrate dose-dependent decreases in heart rate and cardiac index at rest and during exercise, as well as inhibition of the increases in systolic blood pressure, decreases in diastolic blood pressure, and increases in heart rate caused by isoproterenol.[108]

The usefulness of esmolol in myocardial ischemia was also examined. Lange and colleagues investigated the effects of esmolol on size and segmental wall dynamics of reperfused myocardial infarcts in anesthetized dogs. On reperfusion following 3 hours of coronary artery occlusion, functional deterioration was noted in control dogs but did not occur in esmolol-treated dogs.[103] Other investigators also showed that esmolol reduces myocardial infarct size and improves recovery of myocardial function after ischemia.[95] Kirshenbaum and co-workers studied esmolol in 5 patients with acute myocardial infarction, 10 post–myocardial infarction patients, and 4 with unstable angina. Esmolol was given at a dose of 300 μg per kg per min for 420 minutes. Heart rate, systolic arterial pressure, and cardiac index fell during the first 30 minutes of infusion. However, there were no significant additional changes during the maintenance period, nor were there changes in pulmonary capillary wedge pressure or PR interval. Five patients required termination of infusion because of hypotension, and one patient required dopamine to restore hemodynamic stability.[93] Nonetheless, esmolol is safe in this patient population.

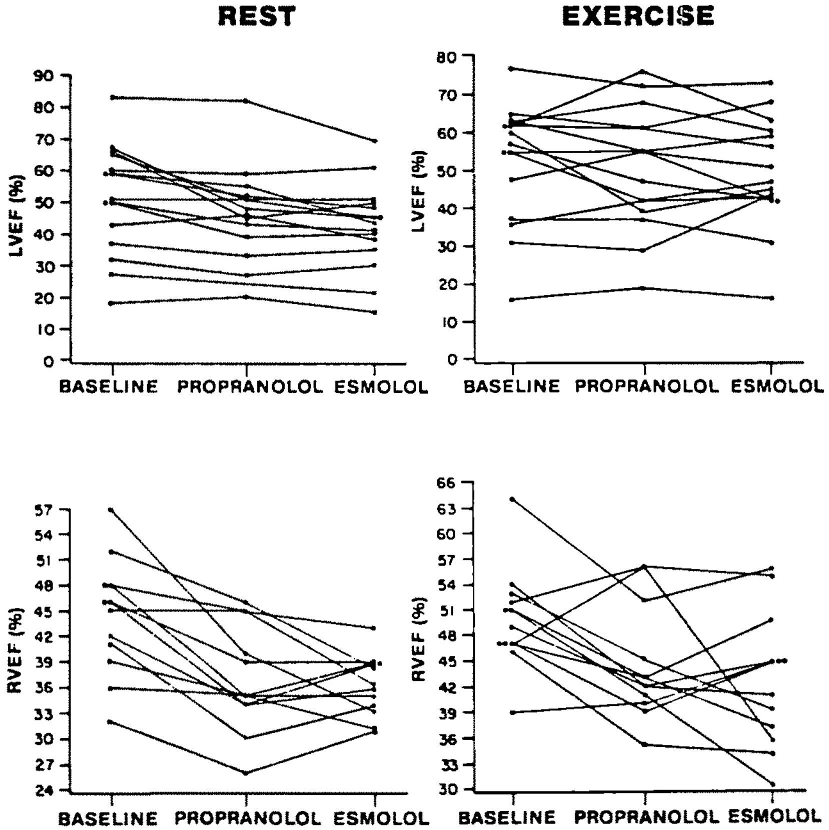

Figure 5. Esmolol and propranolol compared at rest and exercise. LVEF = left ventricular ejection fraction; RVCF = right ventricular contractile force. (*From* Iskandrian A, Bemis C, Hakki A, et al: Effects of esmolol in patients with left ventricular dysfunction. J Am Coll Cardiol 8:225, 1986; with permission.)

Any undesirable hemodynamic effects that may occur are readily reversible by simply discontinuing the drug. However, care should be taken in using esmolol in patients with poor ventricular function, as Iskandrian and associates have shown that esmolol infusion can result in significant further deterioration of cardiac function in this category of patients.[79]

Electrophysiologic Effects

The electrophysiologic effects of esmolol were studied in 14 patients.[67] Like other β blocking drugs, esmolol produces a decrease in sinus node rate and AV conduction. Esmolol prolongs the basic cycle length and sinus node recovery time but does not affect the sinoatrial conduction time or the corrected sinus node recovery time. It does not alter AV nodal refractoriness or retrograde AV nodal conduction time but does increase the cycle length at which Wenkebach periodicity develops.[67] There are no direct effects on atrial conduction or His-Purkinje conduction.[67]

Esmolol has an antiarrhythmic effect in the presence of myocardial ischemia. Intravenous esmolol eliminated spontaneous ventricular fibrillation due to abrupt occlusion of a coronary artery in anesthetized dogs. Esmolol reduced heart rate and had no effect on mean arterial pressure in this study.[62]

Respiratory Effects

The effects of esmolol on respiratory function were studied in 10 patients with mild asthma.[150] Compared with placebo, intravenous esmolol slightly but significantly increased bronchomotor sensitivity to dry air and reduced the sensitivity to isoproterenol. Specific airway resistance values did not significantly differ between esmolol and placebo. In the same investigation, six of the patients entered a similar study using propranolol. Two of these six dropped out after only 1 mg of propranolol because of marked bronchoconstriction. No adverse effects were seen in 60 patients with chronic obstructive pulmonary disease when esmolol was used to treat supraventricular tachydysrhythmias.[108] Thus it appears that esmolol, because of its cardioselectivity, is superior to non-cardioselective β blockers in patients with bronchospastic disease.

Interactions with Anesthetics

It is well known that β blockers and inhalation anesthetics produce additive negative inotropic effects.[78] Studies examined the effects of esmolol on dogs anesthetized with halothane and enflurane.[54,138] The hemodynamic depression caused by esmolol is enhanced by inhalational anesthetics. Adding either enflurane (2.2 per cent) or halothane (1.5 per cent) to esmolol-treated dogs produced decreases in heart rate and marked hypotension compared with esmolol given to awake dogs.[54] The decrease in contractile force was greater than the decrease in heart rate, suggesting a more profound negative inotropic than chronotropic effect. Cardiac output was preserved until the highest doses of esmolol were given.

The hemodynamic effects of esmolol in anesthetized humans depend on several factors. Type of anesthesia, underlying sympathetic tone, concurrent vasoactive drug therapy, intensity of stressful stimulation, and the patients' cardiovascular status all influence esmolol's actions. Esmolol has been used safely in patients anesthetized with diazepam/N_2O, fentanyl, ketamine, thiopental, and enflurane.[31,35,55,57,72,100,118] In diazepam- and enflurane-anesthetized patients given esmolol, blood pressure was lower than in a control group in the absence of changes in systemic vascular resistance, cardiac index, heart rate, and pulmonary capillary wedge pressure, suggesting a negative inotropic effect.[35] In patients anesthetized with high dose fentanyl (75 μg/kg), esmolol increased pulmonary capillary wedge pressure during a stress-free period, also indicating a possible decrease in contractility. Esmolol prevents the tachycardia and attenuates the hypertension associated with ketamine administration, providing a useful anesthetic interaction when these hemodynamic changes are undesirable.[57]

Prior β blockade influences the effects of esmolol. The hemodynamic effects of esmolol were studied in patients not maintained on β blockers.[118] Heart rate responses to intubation were attenuated by esmolol. However, in previously β-blocked patients, esmolol administration resulted in no statistically significant differences in any hemodynamic parameter versus control, except that systolic blood pressure was lower in the esmolol group 5 minutes after sternal spread.[35]

Indications

Perioperative Tachycardia and Hypertension

Esmolol attenuates the undesirable increases in heart rate and blood pressure that occur in response to such stimuli as laryngoscopy and intubation, skin incision, and surgical manipulation.[31,35,55,57,72,100,118] Although tachycardia and hypertension are well tolerated in most patients, they can lead to myocardial ischemia in patients with coronary artery disease.[156] Esmolol has been used to prevent these hemodynamic effects in normal patients,[100] patients with carotid disease,[31] and patients with ischemic heart disease.[55,57,72,118]

Esmolol attenuated the response to intubation in patients undergoing coronary artery revascularization.[55,118] Increases in plasma norepinephrine levels during this period were associated with elevated heart rates in the control group but not in esmolol-treated patients, indicating that esmolol antagonizes the β effects of norepinephrine. Esmolol's effect on heart rate was gone 5 minutes after termination of infusion, confirming its short-lived activity.

Esmolol can be used alone or with vasodilators to treat postoperative hypertension. Because acute systemic hypertension occurring early after cardiac surgery has been linked to catecholamine elevation, a study was performed to evaluate the effects of esmolol in this setting, in comparison with sodium nitroprusside, the conventional therapy.[66] There are several disadvantages to using nitroprusside, including reflex tachycardia, excessive decrease in diastolic blood pressure, and hypoxemia. In a crossover study, esmolol and nitroprusside were titrated, and both equally controlled postoperative hypertension. Esmolol infusion resulted in decreased heart rate, cardiac index, and stoke volume index, and increased right atrial pressure, while nitroprusside caused exactly the reverse hemodynamic effects. In addition, esmolol better maintained oxygenation than did nitroprusside, which caused reductions in PO_2.

Treatment of Arrhythmias

Esmolol is currently approved by the FDA to treat supraventricular tachycardia (SVT) and sinus tachycardia when intervention is appropriate. The drug was used for treatment of supraventricular tachycardia in many studies[45–47,65] and is as effective as propranolol[45] and superior to placebo.[46] Esmolol was infused for 24 hours in 160 patients who had supraventricular tachycardia.[47] Therapeutic response, defined as ≧15 per cent reduction in heart rate or conversion to sinus rhythm, occurred in 79 per cent of the patients. Hypotension was the most common side effect in all studies.[45–47,65] Thirty nine per cent exhibited hypotension, yet 58 per cent of these spontaneously resolved with or without adjustment of esmolol dose. Additionally, it was found that a higher proportion of patients who did not have a history of supraventricular tachycardia but who exhibited supraventricular tachycardia following a surgical procedure responded to esmolol.[47] Gray and colleagues administered esmolol to a group of 11 patients with atrial flutter or fibrillation early after open heart surgery.[65] All patients experienced a 15 per cent reduction in heart rate, and five patients converted to sinus rhythm. Pretreatment with digoxin resulted in a larger proportion of patients achieving therapeutic response. Esmolol and verapamil were compared in patients with atrial fibrillation or flutter. The reduction in ventricular response was similar in both groups. However, 65 per cent of the esmolol patients converted to sinus rhythm, whereas only 30 per cent of patients receiving verapamil converted.[64]

Myocardial Ischemia

β adrenergic blocking drugs are known to be beneficial in myocardial ischemia and infarction, and are widely used in the treatment of angina. Kirshenbaum and co-workers used esmolol successfully in patients with acute myocardial infarction.[93] It was their conclusion that in attempting to use β blockers to reduce myocardial oxygen demand in these patients while avoiding hypotension, heart failure, or conduction abnormalities, esmolol, by virtue of its short duration of action and easy titratability, may be a safer agent in this setting.

Adverse Effects and Complications

By far the most frequently observed adverse effect of esmolol is hypotension. The incidence of systolic blood pressures <90 mm Hg or diastolic values <50 ranged from 11 to 44 per cent.[45,156] This is easily and quickly treated by decreasing or discontinuing infusion of the drug. With hypotension, associated symptoms occurred infrequently: diaphoresis and dizziness (1 to 4 per cent), headache (4 per cent), nausea (2 to 13 per cent), dyspnea (1 to 3 per cent).[36] Angaran and associates[8] reported occasional tissue irritation at the injection site. The recommended dilution of esmolol is ≦10 mg per ml in order to avoid this problem.

Dose and Route of Administration

Esmolol is most widely used with a loading dose of 0.5 mg per kg given over 1 minute, followed by infusions that increase in steps of 50 μg per kg per min every 5 minutes until the desired therapeutic effect is established. Esmolol has also been given as a bolus of approximately 1 mg per kg followed by 150 to 200 μg per kg per min as a continuous infusion.[137] This dose produces a peak effect in about 2 minutes. The effect is gone within 5 to 10 minutes of cessation of therapy. Patients generally respond to doses of esmolol <200 μg per kg per min. Because the solutions for infusion are dilute, large fluid volumes may be administered during prolonged therapy, and alternative β blockers might be chosen for this "chronic" use.

Summary

In conclusion, esmolol is an ultrashort acting cardioselective β receptor antagonist. This property makes its effects easily titratable and particularly suitable for the critically ill patients in need of this kind of cardiovascular intervention, but whose fragile status makes rapidly altered, fine tuning of such therapy an absolute necessity.

LABETALOL

A phenomenon seen commonly in the treatment of hypertension with a pure β or α blocking drug is the development of reflex stimulation of the other receptor subtype (i.e., vasoconstriction after β blockade or tachycardia after α blockade). A drug that provides mild antagonism of both types of adrenoceptors should avoid this problem. Labetalol (Trandate, Glaxo Inc., Normodyne, Schering Corp.) is the representative of such a class of adrenergic blocking drugs that exert an inhibitory effect on both α and β receptors. First described in 1972 by Farmer and colleagues,[49] labetalol was approved by the FDA for both oral and intravenous use in 1984 and has since been used successfully in the treatment of hypertension of various etiologies as well as in the management of angina pectoris.

Physiochemical Characteristics

The chemical designation for labetalol is 5-(1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl) salicamide. The intravenous formulation is a white crystalline powder, dissolved in water and buffered with sodium hydroxide to a pH of 3 to 4. Both methyl- and propylparaben are added as preservatives. The preparation for intravenous use provides a 5 mg per ml solution and is available in 100 mg (20 ml), 200 mg (40 ml, Trandate), and 300 mg (60 ml, Normodyne) ampules. The oral preparation is available in 100, 200, or 300 mg tablets.

Metabolism and Pharmacokinetics

The pharmacokinetic profile of labetalol demonstrates a conformation to a two-compartment open model of distribution and elimination. The apparent volume of distribution is high, estimated at 9 to 16 L per kg, and the protein binding is approximately 50 per cent. Labetalol is a highly polar molecule with a resulting low lipid solubility. It is roughly 7 to 8 times more water soluble than propranolol. On intravenous administration, the drug is rapidly distributed, with an initial phase half-life of 4 minutes. Elimination half-life has been measured from 3.3 to 4.9 hours,[77,91,115] but there can be considerable variability in this parameter.[115] Labetalol is extensively metabolized in the liver to several glucuronides that are subsequently excreted renally. None of the metabolites possesses pharmacologic activity. Only 5 per cent of the unchanged drug appears in the urine. When studied in patients with severe renal insufficiency, no differences in the pharmacokinetic profile of labetalol were noted,[173] suggesting that no modification of dose is needed in renal failure.

The bioavailability of orally administered labetalol is low (30 per cent), owing to first pass intestinal and hepatic elimination. However, advanced age[92] and pre-existing liver disease[77] will markedly increase this percentage. Also, taking the drug with food will increase its bioavailability. Finally, concurrent administration of cimetidine was found to increase plasma levels of labetalol.[34]

Mechanism of Action

Labetalol is a competitive inhibitor of both α and β adrenergic receptors in both *in vitro* and *in vivo* experimental models.[26,49] It causes a concentration-dependent rightward parallel shift in the dose-response curve of isoproterenol in guinea pig atria (β effects) and of norepinephrine in mesenteric vein (α effects).[49] The compound's structure contains two asymmetric centers, thus the molecule can exist as four possible stereoisomers (Fig. 6). The clinical formulation of the drug is a racemic mixture of all isomers. However, only two of these have significant cardiovascular activity, the RR isomer providing the β blocking effect and the SR isomer being responsible for α blockade.[25] Labetalol is a non-selective antagonist of β receptors,[25,49,141] possessing a profile similar to propranolol in this regard. However, its effect on α receptors appears to be specific for the post-junctional α_1 subtype with little or no influence on the presynaptic α_2 receptor.[107] It is less potent than propranolol in its β blockade by a factor of 2 to 4, and is a two- to sevenfold weaker α antagonist than phentolamine.[49,141] The ratio of its own α:β potency is generally accepted to be 1:7 when administered intravenously and 1:3 with oral dosing.[26,90,140,167]

Although initial reports indicated that labetalol was devoid of intrinsic sympathomimetic activity, recent studies suggest that the drug may possess mild agonistic properties at certain β_2 receptor

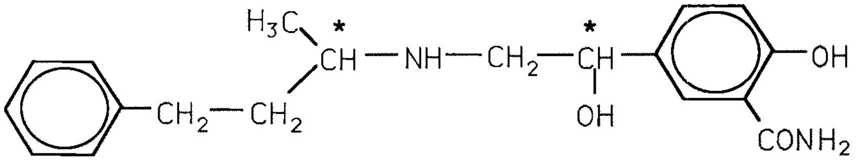

Figure 6. Chemical structure of labetalol. The asterisks denote asymmetric centers.

sites.[28] This might explain some of the vasodilatory capacity of labetalol as well as other effects, such as enhanced glycogenolysis[142] and specific improvement in uterine blood flow.[28]

Like some other β receptor blockers, labetalol possesses membrane stabilizing properties,[29,116] and is also a potent local anesthetic. However, the dose required to elicit these effects is far higher than that used for hemodynamic management. Additionally, in animal studies in which high doses of propranolol and phentolamine were administered, labetalol was found to cause further declines in perfusion pressure at constant blood flow, suggesting that it may possess a direct vasodilator effect.[33]

Hemodynamic Effects

The effect of labetalol on measured hemodynamic parameters is variable and depends on the status of the autonomic nervous system of the subject. When given intravenously to healthy volunteers, labetalol caused either no change or slight decrease in resting heart rate and cardiac index, while leaving peripheral vascular resistance and stroke volume unaltered,[4] suggesting a predominantly β blocking effect in this population. However, in chronically hypertensive patients, most studies describe significant decreases in both systemic and pulmonary vascular resistance with labetalol administration, resulting in a diminution in blood pressure that spared any decrease in resting cardiac output or stroke volume (Table 8).[109] This likely reflects the balanced α and β blockade response in these patients, an effect that sets labetalol apart from the numerous other adrenergic antagonists used for hypertension. Chronic administration of labetalol was associated with a gradual taper or tachyphylaxis of its α blocking effect.[149]

Comparisons of labetalol with propranolol revealed similar effects on heart rate and blood pressure, yet labetalol better maintained cardiac output and decreased systemic vascular resistance, while propranolol resulted in increased resistance measurements.[161] Other studies indicated that labetalol is comparable in effect to combinations of pure α and β blockers[86] or to β blockers combined with direct vasodilators.[12,121]

The hypotensive effect of labetalol has a rapid onset, probably as a result of its effect at the α receptor. Hemodynamic changes appear within 5 minutes and usually peak 10 minutes after an intravenous bolus. Orally administered labetalol has an effect within 2 hours and is maximal at 3 hours.

Table 8. *Hemodynamic Effects of Intravenous Labetalol in Hypertensive Patients*

REFERENCE	NO. PATIENTS	LABETALOL DOSE	POSITION	BLOOD PRESSURE	HEART RATE	CARDIAC OUTPUT	STROKE VOLUME	SYSTEMIC VASCULAR RESISTANCE
Prichard et al[132]	12	0.5 mg/kg	Supine	↓	±	±	±	↓
Joekes et al[85]	14	0.5–1 mg/kg	Supine	↓	±	±	±	↓
Koch[96]	13	50 mg	Supine	↓	±	±	±	±
			Upright	↓	↓	↓	±	↓
			Exercise	↓	↓	↓	↑	↓
Bahlmann et al[10]	9	0.6–1.6 mg/kg	Supine	↓	±	±	±	↓
Svendsen et al[157]	10	50 mg	Supine	↓	±	±	±	↓
			Upright	↓	↓	±	±	↓
			Exercise	↓	↓	±	±	±
Trap-Jensen et al[163]	8	0.75 mg/kg	Supine	↓	±	±	NR	↓
			Psychic Stress	↓	↓	↓	NR	±
Agabiti-Rosei et al[3]	18	100 mg	Supine	↓	↓	±	±	↓
Dunn et al[40]	12	0.5–1 mg/kg	Supine	↓	±	↓	±	±
			45° tilt	↓	±	↓	↓	↑

↓ = statistically significant reduction; ↑ = statistically significant increase; ± = no significant increase; NR = not reported.

Adapted from MacCarthy E, Bloomfield S: Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. Pharmacotherapy 3:193, 1983; with permission

Several studies indicated that labetalol caused a lowering of activity of the renin-angiotensin system.[102,145,162,165] However, in patients whose baseline renin levels were low, labetalol increased their renin activity.[117] The influence of labetalol on this system plays little part in the antihypertensive effect of the drug in the general population. However, one might speculate that patients with hyperreninemic states might particularly benefit from labetalol.

There appears to be no change in cerebral blood flow autoregulation as a result of treatment with labetalol[68] nor is there an alteration in hepatic perfusion.[163] Renal blood flow and glomerular filtration rate are either unchanged or enhanced by the administration of labetalol.[129,135,168]

Electrophysiologic Effects

The electrophysiologic characteristics of labetalol were studied under normoxic and hypoxic conditions in isolated tissues.[166] A decrease in fast inward current during phase 0 of the action potential as well as a delay in all phases of repolarization were demonstrated. Despite this, no evidence of slowing of AV nodal conduction time was found. In another investigation, labetalol in high doses (2 to 5 mg per kg) reduced the frequency of premature ventricular complexes during experimental myocardial ischemia but failed to do so during reperfusion.[131]

Interactions with Anesthetics

Labetalol used in combination with halothane caused additive hypotensive effects. Scott[148] reported that 25 mg of intravenous labetalol with 1 per cent halothane resulted in stable reductions in blood pressure with only mild decreases in stroke volume and cardiac output. This combination of drugs offered smooth control of blood pressure in deliberate hypotensive anesthesia and avoided the reflex tachycardia seen with the use of ganglion blockers or sodium nitroprusside. However, the author warned against adding higher concentrations of halothane (3 per cent), as this predictably resulted in an unacceptable decrease in myocardial performance.

Indications

Hypertensive Emergencies

Intravenous labetalol in small incremental doses rapidly reduces blood pressure in patients experiencing a hypertensive crisis. Moreover, serious side effects sometimes seen during such therapy, such as overshoot hypotension, are rarely observed. Cressman and coworkers[30] described the successful management of 15 of 17 patients in this category using repeated bolus doses of 20 to 80 mg of labetalol at 10-minute intervals. Other investigators have reported similar results using continuous infusions of up to 160 mg per hour of labetalol.[32]

Perioperative Hypertension

Episodes of acute severe hypertension in surgical patients are common occurrences during the perioperative period, especially in patients with pre-existing hypertensive disease. The use of labetalol in the treatment of these events has been investigated. Leslie and colleagues[105] demonstrated that bolus doses of labetalol (0.25 to 0.75 mg per kg) effectively attenuated the rise in rate/pressure product following laryngoscopy and intubation versus a placebo group. The same workers also showed that hypertension in the postoperative period can be reproducibly and safely controlled with intravenous labetalol.[106]

Some patient populations are at added risk of complications from hypertensive episodes. Intraocular pressure is reduced with administration of labetalol,[19] suggesting an important use for the drug in patients with penetrating eye injuries. Patients undergoing coronary artery bypass grafting (CABG) who develop either intraoperative or postoperative hypertension and tachycardia are especially threatened because of the increases that this causes in myocardial oxygen demands. Labetalol has been proven in several studies to be useful in normalizing these parameters both during and after coronary artery bypass grafting.[70,88,122]

Pheochromocytoma

Because of its mechanism of action, labetalol has been tested as a single-agent therapy for patients with pheochromocytoma, and was found to be efficacious in this setting.[159] However, other reports have described hypertensive crises with its administration.[21] This stands to reason, as labetalol's more potent β blocking effect might leave α receptor stimulation relatively unopposed, therefore suggesting that other, more potent α receptor blockade should be utilized prior to labetalol administration under these conditions.

Coarctation

Another application for labetalol in the perioperative setting is the treatment of hypertension associated with aortic coarctation. Jones[87] reported the successful use of labetalol in conjunction with halothane to provide controlled hypotension during coarctectomy. Moreover, since the phenomenon of paradoxical hypertension after surgical repair of this lesion is a function of both sympathetic hyperactivity and hyperreninemia,[158] labetalol, by virtue of its ameliorating effect on both of these processes, may provide a useful treatment modality.

Pregnancy-Induced Hypertension

Hypertension resulting from pregnancy may be one of the best indications for the use of labetalol. Since it is a poorly lipid-soluble drug, placental transfer rate should be low, and studies of fetal blood level of labetalol have proven this to be true.[119] Studies of the drug in this setting have demonstrated its efficacy in reducing maternal blood pressure, while causing no untoward fetal effects.[119,143] There is an increase in uteroplacental blood flow, possibly as a result of intrinsic β_2 stimulation.[142] Also, labetalol may have a beneficial effect on fetal lung maturation.[120]

Angina/Acute Myocardial Infarction

β adrenoceptor antagonists have long been used in the treatment of angina pectoris as a means of reducing myocardial oxygen consumption via decreases in heart rate and contractility. However, there is evidence of the importance of α adrenoceptor–mediated coronary vasoconstriction in all forms of angina,[160] which suggests that a combination α/β blocking drug such as labetalol would be especially advantageous in this population. Studies investigating this question showed that labetalol effectively reduced anginal episodes and improved exercise tolerance in both normotensive[133] and hypertensive[17,27] patients with symptomatic coronary artery disease. Other comparative studies demonstrated that labetalol is at least as effective an antianginal agent as metoprolol, nifedipine, or atenolol.[83,97]

In the treatment of systemic hypertension complicating acute myocardial infarction, Renard and co-workers[136] reported that intravenous labetalol normalized blood pressure and decreased systemic vascular resistance, while decreasing cardiac output only moderately (12 to 17 per cent) in this category of patients. There were decreases in pulmonary capillary wedge pressure only in those patients in whom this measurement was previously elevated. This combination of effects is likely to produce a substantial diminution in myocardial oxygen requirements, and lends support to the use of labetalol in this setting.

Adverse Effects and Complications

Labetalol is relatively free of serious side effects. The most commonly reported unwanted effect has been postural hypotension, a dose-related phenomenon more often seen during intravenous administration. Other adverse effects include fatigue, impotence, scalp tingling, and gastrointestinal disturbances. In large studies of chronically administered oral labetalol, 11 to 30 per cent of patients reported one or more side effects, but the rate of withdrawal from therapy as a result has generally been 7 to 10 per cent.[60,89]

A particular controversy surrounds the use of labetalol in patients with reactive airways disease. Like other non-cardioselective β receptor antagonists, labetalol is capable of diminishing airway conductance. However, its α receptor blocking properties should offset this effect. In studies of healthy subjects, labetalol did not decrease objective measures of respiratory capacity or flow nor did it enhance the bronchoconstrictive effects of histamine, whereas propranolol did in both cases.[110] Similarly, in asthmatic patients, labetalol 20 mg intravenously caused no differences in respiratory function versus placebo.[154] However, the bronchodilatory effects of inhaled albuterol were diminished by concurrent labetalol therapy.[81] In patients with chronic obstructive respiratory disease, the effects of labetalol on respiratory function are variable, with studies revealing either no effect[2] or significant impairment.[7] With this amount of disagreement in the data, most reviewers have recommended that labetalol be avoided in patients with any history of obstructive lung disease.[90,109] Table 9 summarizes the variety of side effects observed with labetalol therapy.

Dosage

The recommendation of the manufacturer regarding dose of labetalol is to carefully titrate the drug to the desired effect in any given individual. The two common means of intravenous administration, continuous infusion or repeated bolus doses, are best accomplished using this approach. Infusion rates should start at 2 mg per min and increase until blood pressure is satisfactorily lowered. Initial bolus dose should be no more than 20 mg over 2 to 4 minutes, with subsequent boluses given in a stepwise increasing dose of 40 to 80 mg. Maximum dose is uniformly reported as 300 mg. Orally administered labetalol should be started at 100 to 300 mg twice or three times daily and increased if needed to a maximum of 3200 mg/day.[90,109,167]

Summary

The previous discussion has indicated that labetalol possesses unique properties that isolate it from categorization with other antihypertensive drugs. By adding this drug to the armamentarium of

Table 9. *Patients Withdrawing During Two-Year Treatment with Labetalol Because of Side Effects*

SIDE EFFECT	NUMBER OF PATIENTS
Dizziness and hypotensive symptoms	20
Tiredness/lethargy	9
Gastrointestinal upset	9
Bronchospasm	9
Headache	6
Skin rashes, all types	6
Visual disturbances	7
Sexual problems	5
Tingling of scalp	4
Allergic reactions	3
Palpitations, chest pain	3
Urinary symptoms	2
Others (one of each)	10
TOTAL	93*

From Gomez G, Phillips L: Labetalol ("Trandate") in hypertension: a multicentre study in general practices. Curr Med Res Opin 6:677, 1980; with permission

*7.2 per cent of 1286 hypertensive patients

Table 10. *New Cardiac Drugs*

	CLASSIFICATION	INDICATIONS	INTRAVENOUS DOSAGE
Amrinone	Inotrope/vasodilator (novel mechanism)	Congestive heart failure with increased vascular resistance	0.75–2.0 mg/kg bolus followed by 5–15 μg/kg/min infusion
Esmolol	Ultrashort acting cardioselective β-blocker	Tachycardia	1 mg/kg bolus followed by 150–200 μg/kg/min infusion
Labetalol	Combined α- and β-non-cardioselective receptor blocker	Hypertension/tachycardia	5–20 mg boluses with stepwise increase, titrating to effect, maximum dose 300 mg

the anesthesiologist, he or she can more effectively treat a wider range and variety of cases of hypertension without impacting on other physiologic parameters, thus optimizing more patients' care.

CONCLUSION

We have discussed several new cardiac drugs, focusing on their respective strengths and weaknesses in the acute care environment. Table 10 summarizes the classification, indications, and dosages of these agents. It is clear that they offer important new dimensions and add breadth to our capacity to provide optimal management of what is becoming a progressively more challenging population of patients with cardiovascular abnormalities.

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What's New in Drugs That Affect the Gastrointestinal Tract?

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Significant morbidity and occasional mortality still occur from the unpredictable event of aspiration.[34] To leave the impression that pharmacologic prophylaxis of aspiration is a substitute for sound judgment and good anesthetic technique would be misleading. The purpose of this article is to review the pharmacology, efficacy, and safety of those drugs that are utilized clinically to alter the volume and/or character of gastric fluid contents. Although not proven, it is hoped that administration of these drugs, by favorably impacting on the factors discussed below, will lessen either the incidence or the severity of aspiration pneumonitis.

FACTORS AFFECTING THE SEVERITY OF ASPIRATION

The acidity of the aspirate is probably the most important factor contributing to the severity of pneumonitis. In numerous animal models, increasing acidity, whether alone or in combination with food particles, results in increasing tracheal mucosal and lung parenchymal damage.[2,67,76] The literature is replete, however, with the suggestion that an aspirate with a pH greater than 2.5 is relatively benign. Several anecdotal reports, as well as recent animal work, tend to refute this concept.[4,62,65] In fact, the initial physiologic derangement may be just as severe and potentially as lethal. Nevertheless, recovery and healing rates appear to be faster if acidity is reduced.

Furthermore, there is the notion that a volume of aspirate less than 0.4 ml per kg (20 to 25 ml in an adult) is relatively safe. Perhaps just as misleading is the converse of this statement—that an aspirate volume exceeding this derived number is uniformly fatal. The concept of a "critical" volume is based on work done in rhesus monkeys in which the aspirated fluid was highly acidic.[56] Work in rats demon-

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strated that the "critical" volume depends on the pH of the aspirate. Even low volumes are associated with a high mortality rate if the pH is low, whereas higher volumes than noted above can be tolerated if gastric fluid is effectively buffered.[37]

Aspiration of particulate matter such as partially digested food particles results in severe pulmonary physiologic derangements.[74] Such aspirates, in addition to increasing shunt fraction and decreasing arterial oxygen tension, often result in alveolar hypoventilation with accompanying hypercarbia. Long term, a granulomatous response develops around these particles. Similarly, bacterial contamination of an aspirate, as may occur in a patient with a bowel obstruction, is associated with a very high mortality rate.[75]

Finally, experience in both fresh and salt water drowning victims demonstrated the importance of the tonicity of an aspirate. Recent work in dogs reconfirmed that as osmolarity of the aspirate increases, so does the degree of pulmonary physiologic derangement.[57] It thus becomes apparent that multiple factors impact on the significance of an aspirate.

WHO IS AT RISK?

One should ask not only who is at risk for aspiration but also who is at risk for developing a severe pneumonitis should aspiration occur. Clinical experience and common sense tell us that the "prepared," fasted adult or pediatric patient presents less risk for aspiration than patients with known anatomic or physiologic disturbances. These latter groups of high-risk patients would include patients with reduced levels of consciousness, difficulties in their swallowing mechanism, esophageal pathology, incompetence of the gastroesophageal junction, delayed gastic emptying, or material in the stomach. A very high percentage of prepared patients, however, come to the operating room with gastric volume and acidity that can result in significant pneumonitis should aspiration occur in the perioperative period (Table 1).[42] One must therefore weigh the unpredictability of aspiration in the perioperative period and the potential beneficial effects of various pharmacologic modalities against the potential risk

Table 1. *Character of Gastric Contents in "Prepared" Patients*

	PEDIATRIC	ADULT	GERIATRIC
Mean gastric pH	1.99	2.40	3.32
% pH <2.5	92	76	60
Mean gastric volume (ml/kg)	0.49	0.37	0.24
% gastric volume >0.4 ml/kg	60	32	12
% pH <2.5 and volume >0.4 ml/kg	60	28	12

associated with the drugs themselves. Is aspiration a preventable iatrogenic event? Does every patient deserve some type of pharmacologic prophylaxis in addition to our best anesthetic technique and judgment?

DRUGS USED FOR PROPHYLAXIS

ANTICHOLINERGICS

Although anticholinergics are of no value in neutralizing acid present in the stomach at the time of their administration, they can block ongoing gastric acid production, which is partially controlled by an acetylcholine effect. Their inclusion with preoperative medicants could conceivably decrease gastric fluid volume and acidity at the time of induction of anesthesia. Their efficacy is dose and time dependent, greatest with glycopyrrolate, and most effective in pediatric and obstetric patients.[3,59,64] Their efficacy in clinically accepted doses in adult patients scheduled for elective surgery is limited. Although potentiation of the inhibitory action of cimetidine on gastric acid secretion by simultaneous administration of anticholinergics was reported in patients with duodenal ulcers, this interaction was not demonstrated in elective surgical patients.[45,55]

For the overall prevention of aspiration, anticholinergics have some potential drawbacks associated with their administration. First, they may decrease lower esophageal sphincter pressure, increasing the likelihood of regurgitation. This detrimental effect is dose related and most pronounced after intravenous administration.[12] Second, anticholinergics can counteract the desirable effects of drugs such as metoclopramide on gastric peristalsis and the lower esophageal sphincter.[11]

ANTACIDS

Particulate antacids are effective in raising gastric fluid pH in a reasonably high percentage of obstetric and surgical patients in elective and emergent situations.[56,66,71] Their effectiveness in raising gastric fluid pH depends on (1) the volume and pH of the gastric contents present at the time of their administration, (2) the frequency and timing of antacid administration, (3) the type and amount of antacid given, (4) what manuevers, if any, are done to promote mixing of the antacid with the gastric contents, (5) the intrinsic gastric motility present at the time of antacid administration, and (6) the rate of ongoing gastric acid production.

Despite their overall effectiveness in raising gastric fluid pH, particulate antacids have come under criticism in the last few years for two primary reasons. First, their administration may increase gastric volume. As an example, routine dosing with antacids every 2 to 4 hours became common practice on many obstetric wards because of the unpredictability of emergency induction of anesthesia as well as concern over acid rebound (an increase in pH over basal levels 4 or more hours following antacid neutralization). This practice fell into disfavor after the discovery that gastric motility in laboring patients slowed[15] (particularly those receiving narcotics for pain). Such a practice could lead to significant increases in gastric volume. Yet, the impact of a single dose of an antacid on gastric volume in an individual patient is highly variable. In patients with reasonably normal gastric motility, antacids may decrease gastric volume because the duodenum can more rapidly accept neutral gastric contents than highly acidic contents.[33]

The second major criticism is that particulate antacid aspiration results in as significant an initial pulmonary derangement as a highly acidic aspirate and in histologic abnormalities that are present as long as 1 month following aspiration.[25] These chronic granulomatous responses were absent in groups with acid aspirates.

Because of these concerns, there is an intense interest in soluble antacids. The two soluble antacids most often investigated clinically to date are 0.3 molar sodium citrate (not available commercially, thus it must be prepared by your hospital pharmacy) and Bicitra (Willen Drug Co). These two antacid preparations contain approximately the same amount of sodium citrate and, despite differing pHs (Bicitra is more acidic since it contains citric acid in addition to sodium citrate), similar neutralizing capacities.[36]

Are these compounds as effective in raising gastric fluid pH as particulate antacids and are there any documented advantages for their use? The preponderance of evidence suggests that soluble antacids are as effective as particulate antacids at raising gastric fluid pH in both elective and emergency surgical patients IF given within 15 to 60 minutes of induction of anesthesia.[16,21,23,26,39,68] In reports in which their efficacy has been questioned, the interval between their ingestion and the induction of anesthesia (gastric sampling) was, as illustrated by the data presented in Table 2, usually greater than 60 minutes.[16,17,28] Recent work demonstrated that if somewhat normal gastric motility is present at the time of antacid administration, the soluble antacids may pass on through the gastrointestinal tract (thus their effect in an individual patient may dissipate quickly), yet gastric acid production is ongoing.[52]

Table 2. *Efficacy of Sodium Citrate (0.3 M, 30 ml) Pretreatment in Elective Cesarean Section Patients*

	CONTROL	SHORT INTERVAL (<60 MIN)	LONG INTERVAL (>60 MIN)
pH <2.5 (%)	100	9	50
Volume >25 ml (%)	64	91	80
Both (%)	64	0	50

Are there advantages in choosing soluble antacids? Soluble antacids mix with gastric contents more readily than do particulate antacids.[30] Thus, there is less reason for the patient to roll from side to side to promote mixing of gastric contents with the antacid. Additionally, some studies indicate that aspiration of soluble antacids, as compared with particulate antacids, though resulting in just as severe initial pulmonary physiologic derangements, may be associated with more rapid recovery and less long-term histologic changes.[19,24]

HISTAMINE H2 RECEPTOR ANTAGONISTS

The H2 blockers decrease nocturnal, basal, and meal-stimulated gastric acid production by competitively inhibiting the action of histamine on the H2 receptor of the gastric parietal cell. In contrast, they have no apparent effect on gastric emptying time or the lower esophageal sphincter pressure. Such findings, as would be expected, sparked an absolute plethora of work on the perioperative efficacy of these compounds in increasing gastric fluid pH or decreasing gastric volume using multiple approaches and in numerous subsets of surgical patients. The following comments attempt to summarize this mass of data on cimetidine (Tagamet—SmithKline & French Lab Co), the most widely studied H2 blocker.

First, the preoperative administration of cimetidine, in a dose-related manner, significantly decreases the acidity of gastric contents in samples taken immediately following the induction of anesthesia.[43] Second, timing of administration is important. Oral administration takes 60 to 90 minutes before a significant effect can be demonstrated, and this effect seems to be waning by 4 to 6 hours.[35] In contrast, intravenous administration is efficacious 45 to 60 minutes following injection, although the duration of action is not necessarily any longer than following oral administration.[10] Parenteral administration results in earlier and higher initial blood vessels and results in a higher percentage of patients with pH values greater than 2.5 at induction of anesthesia compared with oral administration.[70] Finally, multiple-dose regimens (a dose the evening prior to surgery and the morning of surgery) are somewhat more effective than single morning doses.

One- or two-dose oral cimetidine therapy has an excellent safety record. Such short-term administration, however, is reported to inhibit the mixed function oxidase system and to decrease liver blood flow.[5,20] These effects can result in higher blood levels and more pronounced effects of drugs that depend on the liver for their clearance. Indeed, the co-administration of cimetidine will prolong the elimination half-lives of warfarin, diazepam, theophylline, phenytoin, and possibly propranolol. Likewise, there are a few reports in which cimetidine contributed to delayed awakening from anesthesia by this mechanism.[40,69] There is a theoretic, if not real, concern that cimetidine therapy can aggravate bronchospasm in asthmatics by allowing histamine to have an unopposed H1 effect.[49] Finally, rapid intravenous administration of relatively large doses (600 mg) of cimetidine causes hypotension and significant dysrhythmias.[9]

Cimetidine is very safe in obstetric patients. Two major reports demonstrated no maternal complications attributable to cimetidine treatment nor were any adverse effects noted in infants whose mothers received cimetidine (based on Apgar and neurobehavioral scores).[29,38]

Does the newly available H2 antagonist—ranitidine (Zantac—Glaxo)—offer any significant advantages over cimetidine? Purported advantages are ranitidine's greater potency, longer duration of gastric antisecretory effect (6 to 8 hr), lower incidence of side effects, and lesser degree of inhibition of the mixed function oxidase system.[5] Its onset of action is similar to that of cimetidine and therefore it suffers from the same limitations in the emergent situation. Its efficacy in raising gastric pH is similar to or slightly better than that of cimetidine (Table 3).[13,18,22,48] The prolonged duration of action is well documented and conceivably offers a distinct advantage. A dose on the eve of surgery should suppress acid production throughout the night, while a morning dose should be of long enough duration to provide good conditions well into the emergence/recovery period. The recent claims of fewer side effects and less inhibition of the mixed function oxidase system may be overstated, although to date clinical experience tends to support this conclusion.[46]

Famotidine (Pepcid—Merck, Sharp, and Dohme), a propanimidamide derivative, is the latest H2 receptor antagonist to enter the market. Clinically used dosages suppress acid production for 10 to 12 hours. Intravenous administration may be associated with a slightly faster onset of antisecretory effect (30 min) compared with other H2 receptor antagonists. Systemic effects of famotidine in the central nervous, cardiovascular, respiratory, or endocrine systems have been neglible to date, and minimal drug interactions have been identified in clinical trials. To date, studies employing famotidine for aspiration prophylaxis are lacking.

Co-administration of antacids or metoclopramide with H2 blockers reduces the bioavailability of the H2 antagonist secondary to reduced absorption.[27,47] Nevertheless, co-administration of H2 blockers and metoclopramide, in a number of studies, had a greater

Table 3. *Comparison of Cimetidine and Ranitidine as Prophylaxis Against Gastric Aspiration Syndrome*

	VOLUME OF ASPIRATE (ML)	PH	BOTH (%)
Placebo	20 ± 6	2.3 ± 0.3	87
Cimetidine (300 mg PO)	16 ± 2	4.0 ± 0.5	29
Ranitidine (150 mg PO)	7 ± 2	6.1 ± 0.5	15

efficacy in favorably altering both the pH and volume of gastric fluid than either drug alone.[41,44,54,63]

METOCLOPRAMIDE (REGLAN—A. H. ROBINS)

Metoclopramide is a chlorbenzamide derivative that possesses three characteristics that make it potentially very useful in anesthesia. It increases the lower esophageal sphincter pressure, speeds gastric emptying time, and has antiemetic properties.[1,61] It has no direct effect on gastric fluid pH. As such, it represents a markedly different approach to aspiration prophylaxis than the drugs discussed above.

Several investigators have noted that both oral and parenteral administration of metoclopramide to patients scheduled for elective or emergency surgery decreased the volume of gastric contents (Table 4).[14,31,51,73] Others have been unable to duplicate these findings.[8] Some of these discrepancies may be explained by variations in dose and timing of administration. Another factor is the highly variable blood levels attained following oral administration due to the wide range in first pass hepatic metabolism of metoclopramide. Differences in observed effects may also be due to differences in the basal state of gastrointestinal motility present at the time of administration of metoclopramide. It is probable that metoclopramide is most effective in modifying gastric motility when it is already impaired by other factors. Of interest to anesthesiologists is the observation that metoclopramide may not reliably reverse narcotic-induced inhibition of gastric mobility.[50] Similarly, metoclopramide may be more effective at emptying a "light" or liquid meal than a solid meal.[32] Although a significant decrease in gastric volume can be demonstrated within 20 minutes of administration of metoclopramide, it is recommended to wait at least 30 minutes after a "light" meal and up to 75 to 90 minutes after "heavier" meals for a reliable effect.

Likewise, metoclopramide increases lower esophageal sphincter pressure and barrier pressure (the pressure difference between intragastric pressure and lower esophageal sphincter pressure) in both

Table 4. *Efficacy of Metoclopramide in Pediatric Patients Admitted for Emergency Surgery*

	METOCLOPRAMIDE	PLACEBO
Gastric Volume		
Mean	25 ml	48 ml
Range	0–105 ml	0–271 ml
>0.5 ml/kg	11/29	21/29
pH <2.5 and volume >0.5 ml/kg	2/29	6/29

nonpregnant and pregnant women with and without symptoms of esophageal reflux.[6] Thus, the likelihood of passive regurgitation should be reduced following metoclopramide. The efficacy of metoclopramide as an antiemetic in anesthesia is highly variable.

In the dose range commonly employed (10 to 20 mg), metoclopramide is relatively safe. Higher dosages, particularly in children, are associated with agitation, irritability, confusion, and extrapyramidal symptoms.[53,60] There are also isolated reports of hypotension and dysrhythmias, including complete heart block, associated with parenteral metoclopramide.[72] To date, when given to parturients, metoclopramide does not impede the progress of labor nor adversely affect Apgar or neurobehavioral scores.[7] Finally, clinical studies are now under way investigating the efficacy of several new gastric and intestinal prokinetic drugs.[58]

SUMMARY

Administration of both soluble antacids and H2 histamine receptor antagonists effectively increases gastric fluid pH in the perioperative period. In the emergent situation, soluble antacids effectively buffer gastric acid more rapidly than do H2 histamine receptor antagonists. Metoclopramide and newer gastrokinetic drugs decrease gastric volume if given pre induction in adequate doses. Such drugs may be particularly useful in emergent situations. These drugs are, however, no substitute for good judgment and proper anesthetic technique.

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What's New in Psychotropic Agents in Anesthesia?

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According to *Webster's Dictionary*, "psychotropic" means "having an altering effect on the mind." Thus most if not all medications used by anesthesiologists may fall into this category. "New" is a relative term, but the present speed with which new pharmaceutical products are being introduced means that new drugs get old very quickly. In this chapter we will deal with psychotropic drugs that were introduced quite recently, including some promising new drugs that have not yet been approved by the United States Food and Drug Administration (FDA).

BROAD CATEGORIES OF PSYCHOTROPIC DRUGS

In a broad sense all drugs acting on the central nervous system should be included as psychotropic agents like sedative drugs, tranquilizers, hypnotics, analgesics, narcotics, general anesthetics, hallucinogens, alcohols, stimulants, anticholinergics, and others.

Barbiturates are a classic example of sedative/hypnotics. They have been in use in medical practice for many years. However, there are no new barbiturates of major interest to the anesthesiologist. The second group of sedative/hypnotic/tranquilizers are the *benzodiazepines*. Diazepam is considered the prototype in this group. These relatively new agents all contain a benzodiazepine ring in their structure, but various modifications of the original form resulted in numerous new compounds with vastly different pharmacokinetic, pharmacodynamic, and pharmacologic profiles. The newer agents in this category are midazolam, triazolam, and temazepam. *Narcotics/analgesics*, although primarily used to control pain, have strong psycho-

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tropic properties. The older pure μ agonists in this group (especially morphine and meperidine) allegedly possess euphoric and occasionally dysphoric properties. However, these effects are rather inconsistent and cannot be relied upon for clinical advantage. Several new and potent synthetic opiate receptor agonists have become available recently; fentanyl is the parent compound in this group. Anesthesiologists use synthetic narcotics quite extensively. New additions to this group are sufentanil and alfentanil. Several new *agonist-antagonist* analgesics have appeared on the horizon. The oldest drug in this group is pentazocin, which has largely been given up by physicians because of the associated high incidence of psychotomimetic side effects. However, newer compounds in this group, namely nalbuphine, butorphanol, buprenorphine, and dezocine (the last one yet to be approved by the FDA), seem to have fewer side effects.

To treat anxiety disorders, psychoses, and mood disorders, psychiatrists and anesthesiologists involved with pain management clinics use a broad array of drugs: *phenothiazines* such as chlorpromazine and promethazine; *butyrophenones* such as haloperidol and droperidol; *tricyclic antidepressants* like imipramine and amitriptyline; *monoamine oxidase inhibitors* such as tranylcypromine and phenelzine; *lithium salts;* and others. These medications, mostly used for psychiatric disorders, have fairly well-defined actions and interactions with the general anesthetic agents. *Ketamine,* a phencylidine derivative, is an old but still poorly understood anesthetic agent with limited use because of the high incidence of postoperative hallucination and agitation.

General anesthetic agents, both intravenous and inhalational, obviously have strong and sometimes prolonged psychotropic effects. Some newer intravenous anesthetic agents are etomidate (an imidazole derivative), midazolam (a water-soluble benzodiazepine), and propofol (diisopropylphenol, not yet approved by the FDA). New inhalation anesthetic agents are isoflurane and sevoflurane (the latter not yet approved by the FDA). So-called "recreational" drugs such as *alcohol, marijuana, codeine, PCP (phencyclidine derivatives),* and others have profound altering effects on the mind and must be included among psychotropic drugs.

Detailed description of all the psychotropic agents mentioned above is beyond the scope of this chapter. New inhalation anesthetic agents, new non-opioid intravenous agents, and new analgesics and narcotics will be discussed in articles elsewhere in this issue. Here we will confine our discussion to the newer drugs used for premedication and for conscious sedation.

IDEAL PREMEDICATION

Lorenzo Bruno of Turin, Italy, first used large doses of morphine as premedication in 1850. Later, when the famous French physiologist Claude Bernard endorsed the idea, the use of premedication before anesthesia became a standard practice. The primary reason why premedicants were used during the early days was to make anesthesia safer. Morphine premedication reduced the need for excessive doses of chloroform and fewer patients died of chloroform poisoning. The objectives of premedication changed over time but relief of preoperative anxiety has always been one of the most commonly cited objectives. But *do* the commonly used premedicants predictively reduce patients' subjective anxiety?

In a classic paper, Egbert and co-workers[15] reported that patient anxiety was reduced more by an anesthesiologist's visit and an explanation of anesthetic procedures than by premedication with pentobarbital. More recently, Forrest and colleagues[16] found that none of the six commonly used premedicants given intramuscularly reduced patient anxiety any better than a placebo, although some of the premedicants did make the patients drowsy. Since patient anxiety is a subjective feeling and rather difficult to measure, many investigators tend to equate drowsiness with lack of anxiety. This assumption can be wrong because a very sleepy patient could still be extremely anxious. Patients whose level of consciousness is deliberately dulled by the use of excessive premedicants may indeed be oblivious to their anxiety. However, the price patients pay for heavy premedication is prolonged drowsiness, respiratory depression, dizziness, sometimes nausea and vomiting during the postoperative period, and inability to participate in their own postoperative care. The combined residual effects of long-acting premedicants and general anesthetic agents are responsible for many of the undesirable depressant effects in the postoperative period. Some of the newer premedicants with quick onset, short elimination half-life, and a high clearance rate may circumvent some of the problems associated with the traditional longer-acting premedicants. Amnesia concerning events on the day of the operation, and sometimes even the day after the operation, is not necessarily in the patient's interest. However, some overly anxious patients often mistakenly believe that amnesia is a way to escape from anxiety, and demand to be amnesic. Instead of educating the patient about the inadvisability of prolonged amnesia, many anesthesiologists tend to oblige the patient by routinely prescribing a long-acting amnesic agent. Without getting into the controversy of whether an amnesic agent is desirable or not, we have the capability to provide and almost tailor an amnesic period for an individual patient, using the newer benzodiazepines.

Following are short descriptions of several new drugs used as premedicants.

MIDAZOLAM (Versed, Roche)

Diazepam, one of the early benzodiazepines, not too long ago claimed the distinction of being the number one prescription drug in the United States. Because of its excellent anxiolytic and amnesic properties of short duration, diazepam is still the most common premedicant used all over the world. However, both oral and parenteral preparations of diazepam have several problems, many of which are related to its insolubility in water. The solvent used for diazepam (and also for a more recent benzodiazepine, lorazepam), propylene glycol, causes pain on injection (both intramuscular and intravenous) and a very high incidence of thrombophlebitis.[26,45] The other problems with diazepam are its long elimination half-life, its slow rate of clearance from the body (Table 1) and the presence of active metabolites that have equally long elimination half-lives. Thus, with repeated doses, diazepam easily accumulates in the body adds to the residual effects of general anesthetics and narcotic agents used during the perioperative period.

Lorazepam, because of its shorter elimination half-life and absence of active metabolite, has a more favorable pharmacokinetic profile (Table 1) but clinically its duration of action is very long, much longer than diazepam. This makes lorazepam undesirable for patients undergoing operations of short or intermediate length. Lorazepam shares with diazepam a high incidence of thrombophlebitis after intravenous use, although intramuscular injection is not as painful.

Midazolam hydrochloride, a 1,4 benzodiazepine derivative, is a unique recent addition to the benzodiazepine family. As the first water-soluble benzodiazepine, midazolam represents an important therapeutic addition to drugs used in anesthetic practice.[19,27] An imidazole ring fused in position 1,2 distinguishes midazolam from other injectable benzodiazepines (Fig. 1). Unlike the diazepine ring of older benzodiazepines, the imidazole ring of midazolam is basic, with a pKa of 6.15, thus allowing preparation of water-soluble salts with hydrochloric, maleic, and lactic acids. A unique feature of midazolam is a pH-dependent equilibrium between the open-ring and closed-ring forms of the molecule (Fig. 2). When the environmental pH is less than 4, the imidazole ring opens between positions 4 and 5 to form a stable water-soluble derivative. When the pH is greater than 4, as inside the body, the ring closes to form a molecule with increased lipophilicity. Unlike injectable diazepam and lorazepam, which are not water soluble and are dispensed in propylene glycol as a solvent, midazolam does not hurt when injected intravenously or intramuscularly. The incidence of thrombophlebitis is extremely low following midazolam compared to diazepam and lorazepam.

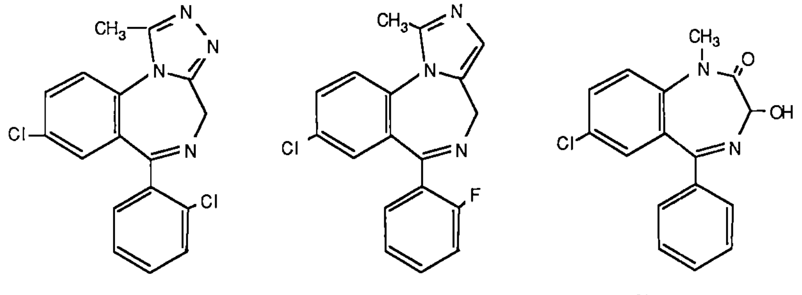
Initially it appeared that midazolam was approximately twice as potent as diazepam. After some experience with the agent, many clinicians now believe the dose-response curves of diazepam and midazolam are not parallel; at higher dose levels midazolam is probably three to four times more potent than diazepam.

Midazolam's Mechanism of Action

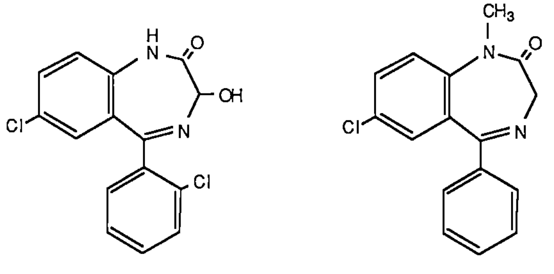
Like many other benzodiazepine drugs, midazolam has a high binding affinity to benzodiazepine receptors in the brain, where it

Table 1. *Pharmacokinetic Variables of Midazolam, Lorazepam, Diazepam, Temazepam, and Triazolam*

VARIABLE	DIAZEPAM	LORAZEPAM	MIDAZOLAM	TEMAZEPAM	TRIAZOLAM
Distribution half-life (min)	37–78	1.1–4.3	5.7–10.1	21–98	2.8–8
Elimination half-life (hr)	20–40	10–20	2–4	7–33	1.4–3.9
Volume of distribution (L/kg)	0.71–1.5	0.6–2.0	0.53–2.9	0.57–2.8	0.8–1.3
Clearance (ml/kg/min)	0.25–0.5	0.75–1.5	6.0–12.0	0.59–2.5	1.4–10.4
Protein binding (%)	98–99	88–92	92–97	96–98	89–94
Active metabolites	Yes	No	Yes, but not significant	Yes, but not significant	Yes, but not significant



Triazolam **Midazolam** **Temazepam**



Lorazepam **Diazepam**

Figure 1. Chemical structures of diazepam, lorazepam, midazolam, temazepam, and triazolam.

facilitates the action of gamma-amino-butyric acid (GABA). GABA, one of the most important inhibitory neurotransmitters in the central nervous system (CNS), inhibits neuronal firing and reduces CNS excitability by increasing permeability of the neuronal membrane to chloride. It is postulated that midazolam binds to a receptor complex in the postsynaptic nerve cell membrane, but the exact mechanism of the drug-receptor interaction is not completely understood. The sed-

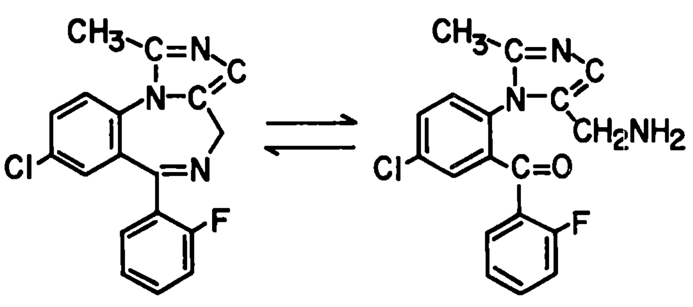


Figure 2. The schematic diagram shows pH dependent open and closed ring formations of midazolam.

ative and anticonvulsant effects are believed to be related to the potentiation of GABA binding to its own receptor to increased chloride ion influx. This prolongs hyperpolarization of the neuron, resulting in inhibition of neuronal transmission.[39] Its anxiolytic and muscle-relaxant actions are probably mediated through the activation of glycine.[50] Benzodiazepines are known to increase the availability of glycine, another inhibitory neurotransmitter in the brain. The mechanism of the amnesic action of benzodiazepines is still poorly understood. Skeletal muscle relaxation effects may also reflect actions on spinal internuncial neurons.

Pharmacokinetics of Midazolam

Following oral administration, midazolam is absorbed rapidly, with a peak concentration occurring in 15 to 50 minutes. Bioavailability after oral administration is only 31 to 72 per cent because of extensive first-pass hepatic extraction. Pharmacokinetic parameters are shown in Table 1.[2,24,27,48] After an intramuscular injection, midazolam's bioavailability is much higher (91 per cent). Following intravenous administration, the onset of clinical effect is very rapid because of the drug's high lipophilicity. The partition coefficient of midazolam between n-octanol and phosphate buffer is 475, which approaches that of diazepam (580) and is much higher than that of lorazepam (73) or temazepam (62).[21] The onset of sedative and anxiolytic effects occurs within 5 to 10 minutes after intramuscular injection and 1 to 2 minutes after intravenous administration. Midazolam has a high intrinsic affinity for benzodiazepine receptors in the brain. Its rate constant for association (^{K}RA) is 654 per hr as compared to 573 per hr for diazepam and 21 per hr for lorazepam.[25] High receptor affinity and high lipophilicity thus account for the more rapid onset of action of midazolam compared with diazepam and lorazepam.

Midazolam has a short distribution half-life and the plasma concentration–versus-time curve is characterized by a biexponential equation (Fig. 3). The drug is extensively bound to plasma proteins, predominantly to albumin; only 3 to 6 per cent of the drug is unbound. Changes in protein binding, therefore, can markedly influence the response to a given dose and cause unpredictable results by changing the unbound fraction of drug. The total body clearance of midazolam (6.0 to 12.0 ml per kg per min) is high and exceeds that of other benzodiazepine drugs. Midazolam is metabolized by hepatic microsomal oxidation; less than 0.5 per cent of a dose is excreted unchanged in the urine. The major metabolite, α-hydroxymidazolam, has 1/10 to 1/40 the activity of the parent compound but is rapidly glucuronidated. Its overall contribution to physiologic effect is negligible after intravenous administration. The clearance of midazolam is affected by changes in hepatic blood flow; changing the patient to a supine position increases clearance. In elderly males and in patients with cirrhosis, clearance is significantly decreased.[31] Therefore, caution is necessary when midazolam is administered to patients with

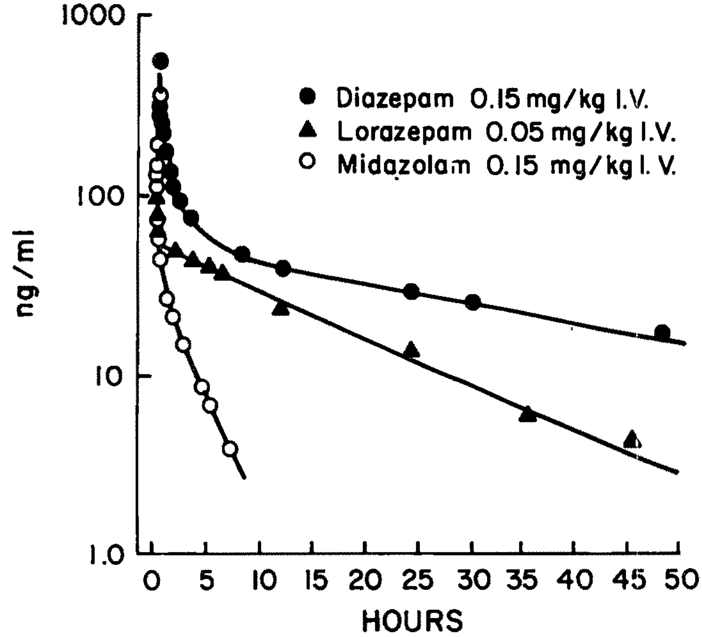


Figure 3. Pharmacokinetic profiles of diazepam, lorazepam, and midazolam. (*From* Stanski DR, Walkins WD: Benzodiazepines. *In* Kitz RJ, Laves MD (eds): Drug Disposition in Anesthesia. Philadelphia, PA, Grune & Stratton, 1982, pp 173–191; with permission.)

liver disease. Renal failure does not alter the clearance of unbound drug; however, recovery from midazolam-induced anesthesia has been reported to be prolonged in patients with renal failure.[55]

The elimination half-life of midazolam ranges from 2 to 4 hours and is much shorter than that of diazepam and lorazepam. The half-life may be prolonged in elderly patients.[20] Metabolism, however, does not adequately predict the duration of action of midazolam when administered parenterally in single doses. Initially, drug redistribution from brain receptor sites to peripheral tissue plays a more important role in terminating drug action. The rate constant of midazolam for dissociation from the benzodiazepine receptor is high (2.09 per hr); it approaches that of diazepam (2.85 per hr) and is much higher than lorazepam (0.30 per hr).[25] This factor, along with a high metabolic clearance, short terminal half-life, and high lipophilicity, results in a short duration of action and rapid recovery, providing midazolam with a substantial advantage over diazepam and lorazepam when used for premedication.

There is a good correlation betwen midazolam serum concentrations and its pharmacologic effects. Because individual responses vary widely, measurement of serum drug levels is not clinically useful to monitor therapy.[2,9]

Midazolam as a Premedicant

The oral form of midazolam is not available in the United States although it has been used in Europe. Midazolam works as an excellent premedicant both by intramuscular and intravenous routes. Intranasal administration of midazolam is being tried in the pediatric age group. Fragen and co-workers[17] compared midazolam 0.08 mg per kg^{-1} with hydroxyzine hydrochloride 1.5 mg per kg^{-1}. Each drug was given intramuscularly either alone or with atropine sulphate 0.4 mg or scopolamine hydrobromide 0.4 mg. Midazolam produced quicker onset of action, greater anxiolysis during the first 30 minutes, and greater amnesia and had a higher overall rating by the patient. However, Artru and co-workers[4] compared a similar dose of midazolam with a placebo (midazolam vehicle) using the Anxiety Visual Analogue Test (AVAT) scoring system and found no significant difference between midazolam and placebo in relieving patient anxiety. They did, however, find significantly more sedation after midazolam. Conner and colleagues[8] reported that midazolam 5 mg given intravenously to adult surgical patients reduced subjective anxiety scores.

All benzodiazepines cause anterograde amnesia, especially when given intravenously, but retrograde amnesia has not been reported. Connor and associates[8] and Dundee and Wilson[13] reported profound anterograde amnesia after intravenous administration of midazolam, characterized by short latency (2–3 min), high frequency (80–90 per cent), and relatively short duration (20–30 min). This time course of amnesia is similar to that of diazepam (Dundee and Pandit[12]) but quite different from lorazepam's long latency (15–20 min), high frequency (70–80 per cent), and a long duration of action (4–6 hr).[35] Figure 4 compares the anterograde amnesic effects of diazepam, midazolam, and lorazepam after intravenous administration of equipotent doses.[11] Midazolam, unlike diazepam, causes significant amnesia even after intramuscular administration.[17]

Although most premedicant studies published so far described midazolam's use intramuscularly, more anesthesiologists are using it intravenously for premedication. Intravenous premedication has the distinct advantage of quick action, precise timing for therapeutic effects, useful effect after a smaller dose, and more predictable anterograde amnesia. Since midazolam has a short elimination half-life (compared with other benzodiazepines), there is less reluctance to repeat the doses if it becomes necessary. The use of midazolam as an intravenous premedicant thus contributes to the quick overall recovery of patients after anesthesia. More anesthesiologists are willing either to omit the traditional oral or intramuscular premedicant altogether or to use smaller doses of those long-acting agents and supplement with intravenous midazolam if necessary. This trend holds true for outpatient as well as inpatient surgery.

The dose of midazolam for intramuscular premedication is ap-

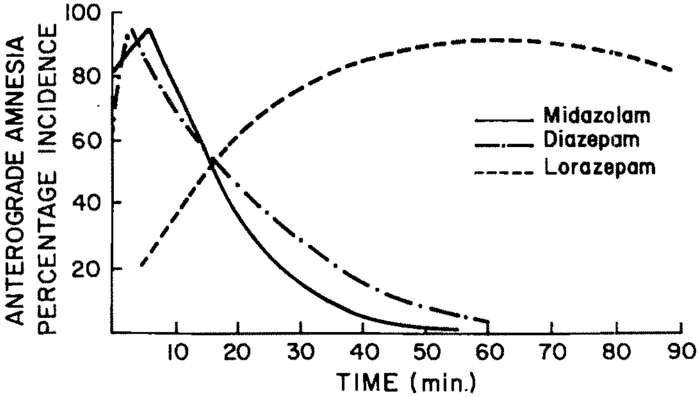


Figure 4. Time course of anterograde amnesia effects of diazepam (10 mg IV), lorazepam (4 mg IV), and midazolam (5 mg IV). (*From* Dundee JW, Halliday N, Harper KW, et al: Midazolam. A review of its pharmacological properties and therapeutic use. Drugs 28:519–543, 1984; with permission.)

proximately 0.1 mg per kg^{-1} (0.07 to 0.12 mg per kg^{-1}). The dose must be reduced significantly in older individuals, patients with hypovolemia, reduced serum protein and poor renal function. The initial intravenous premedicant dose in young, healthy adults ranges from 1 mg to 2.5 mg. This dose can be repeated if necessary. For elderly patients a dose of 0.5 to 1.0 mg intravenously has been recommended as the initial dose. If a narcotic premedicant is used, the doses of midazolam just recommended for young and older adults should be further reduced by half. The initial intravenous dose of midazolam for children ranges from 0.05 to 0.1 mg per kg^{-1}. In a preliminary study, midazolam at a dose of 0.2 mg per kg^{-1} has been found to be effective as a premedicant when given intranasally to children (Leigh J, et al, University of Michigan Medical Center, Ann Arbor, Michigan, personal communication).

Use of Midazolam for Conscious Sedation

Midazolam will be most used to achieve conscious sedation in patients undergoing operations or diagnostic procedures under local, regional, or topical anesthesia. An ideal sedative hypnotic should provide a calming effect, possibly analgesia, anterograde amnesia of short duration, and possibly euphoria. It should depress coughing, gagging, and laryngospasm (especially for procedures involving the oral cavity or orpharynx); yet it should leave the patient cooperative and produce only minimal depression of the central nervous, cardiovascular, and respiratory systems. Recovery should be prompt, without adverse effects or residual drowsiness. Midazolam, though not an analgesic, fulfills many of these desirable criteria, especially when combined with a potent analgesic like fentanyl, sufentanil, or alfentanil.

Ketamine, an excellent analgesic, is seeing a resurgence in use in combination with midazolam to supplement regional or local anesthesia.[56] Ketamine in small initial doses of approximately 1.0 mg per kg^{-1}, with midazolam 0.05 to 0.2 mg per kg^{-1}, provides excellent analgesia, amnesia, and a calming effect. The incidence of undesirable side effects of ketamine, such as excitement, hallucination, and bad dreams, is very low with this combination.

TEMAZEPAM (Restoril, Sandoz)

Temazepam, 4-hydroxydiazepam (see Fig. 1), is commercially available in two different pharmaceutical oral dosage forms: as a hard gelatin capsule and as a solution in polyethylene glycol within a soft gelatin capsule. Pharmacokinetic parameters are shown in Table 1. The rate of absorption differs with the two dosage forms. Fucella and co-workers,[18] in a study comparing the absorption and bioavailability of temazepam in hard and soft gelatin capsules, found that absorption from soft gelatin capsules was significantly faster and produced earlier and higher peak plasma concentrations. Peak plasma values were obtained within 0.83 hours following ingestion of the soft capsule and within 1.44 hours after the conventional hard capsule. A rapid rate of absorption from the soft capsule was associated with a rapid onset of drowsiness. Peak plasma concentration of temazepam was also higher after administration of soft capsules (0.892 μg per ml) compared with the hard capsules (0.668 μg per ml). There were no differences in relative bioavailability of the two formulations, and elimination half-life of temazepam in the soft gelatin capsule (8.35 hr) was not significantly different from the hard capsule (7.25 hr). Earlier data on temazepam suggested a short half-life of 5 to 8 hours; more recent information, however, indicates a half-life ranging from 7 to 33 hours.[33,49]

The effects of age and gender on the pharmacokinetics of temazepam have been studied. Smith and colleagues,[49] in a study with 30 healthy male and female volunteers aged 20 to 78 years, found that age had no significant effect on the pharmacokinetics of temazepam in male subjects. Elimination half-life, however, was significantly prolonged in elderly women (18.4 hr) as compared with middle-aged women (10.2 hr) or young women (11.5 hr). The apparent volume of distribution in young women (1.33 L per kg) was significantly greater than in middle-aged women (0.88 L per kg). In elderly patients, elimination half-life was significantly longer in women (18.4 hr) than in men (9.9 hr). A longer elimination half-life and reduced clearance of temazepam in elderly women resulted in increased drug accumulation after multiple dosing. This could result in untoward daytime sedation in this group of patients.

Temazepam is metabolized in the liver primarily by glucuronide conjugation. Following oral administration, approximately 8 per cent of the drug is metabolized on the first pass through the liver. There are two reported metabolites, both having an elimination half-life of 2 hours; however, their overall contribution to the pharmacologic effect of temazepam is not clinically significant. One of the metabolites of temazepam is oxazepam, which is an active agent, but the quantity of oxazepam as a metabolite is not excessive.[23]

The effect of liver disease on the disposition of temazepam was studied by Ochs and associates[33] in nine patients with cirrhosis. Following a single oral dose, peak serum concentrations of temazepam were reached later in patients with cirrhosis compared with a control group (2.9 hr vs. 0.6 hr). The volume of distribution was smaller and the elimination half-life of temazepam was shorter in patients with cirrhosis (10.6 vs 14.6). However, differences were not statistically significant in clearance between patients with cirrhosis and controls. Thus slower absorption of temazepam in patients with cirrhosis may lead to a delayed onset of action, but the rate of elimination and the extent of accumulation are not altered when compared with healthy persons of similar age and sex. Based on the pharmacokinetics, dosage changes are therefore not necessary in patients with cirrhosis.

Concomitant use of oral contraceptives has recently been reported to alter the disposition of temazepam. Stoehr and coworkers[53] studied the effects of low-dose estrogen oral contraceptives on the elimination of temazepam. In two parallel crossover studies with 40 patients, women taking oral contraceptives and a control group who had not taken oral contraceptives both received a single 30-mg oral dose of temazepam. The elimination half-life decreased in the oral contraceptive group compared with the control (8.0 hr vs. 13.3 hr); clearance rose from 0.87 to 1.41 ml per min per kg, and the area under the plasma concentration time curve (AUC) decreased significantly for users of oral conceptives. Elimination of temazepam was markedly increased in oral contraceptive users. Hence, the steady-state concentrations of temazepam may be achieved more rapidly and be lower in patients using oral contraceptives. Consequently, the usual 30-mg dose of temazepam may be less effective as a sedative/hypnotic for women who use oral contraceptives.

TEMAZEPAM AS A PREMEDICANT

Temazepam has been used as a hypnotic for the short-term treatment of insomnia. However, only a few trials in the United States have evaluated its potential use as a premedicant.

Clark and colleagues ,[7] in a double-blind randomized trial, compared temazepam with diazepam or a placebo as premedication in 145 elderly men undergoing minor urologic surgery. Patients received either diazepam 10 mg, temazepam 20 mg, or a placebo. Both onset of sedation and postoperative recovery following anesthesia were significantly more rapid in the temazepam group than in patients receiving diazepam. Amarasekera,[3] in a study with 100 female patients undergoing minor gynecologic surgery, compared temazepam 30 mg with diazepam 10 mg as premedicants given orally 1 to 5 hours preoperatively. The sedative effect of temazepam was found to be superior to that of diazepam, using both objective and subjective criteria for assessment. Temazepam was also significantly better than diazepam in relieving preoperative anxiety. O'Boyle and associates[32] compared the rapidity of onset and degree of anxiolytic activity following oral administration of temazepam with intravenous administration of diazepam. The study design was randomized and double-blind; 39 patients undergoing oral surgery received either temazepam 40 mg (soft gelatin capsule) orally followed at 35 minutes by intravenous saline, or an oral placebo followed at 35 minutes by intravenous diazepam 10 mg. The onset of anxiolysis was rapid with temazepam, and a significant reduction in the anxiety level occurred at 30 minutes. Anxiety control and patient cooperation were comparable to those seen with intravenous diazepam. Little amnesia was seen for perioperative events following either of the treatments. Sedation obtained was similar with both treatments.

Beechey and co-workers[6] compared temazepam 20 and 30 mg orally with placebc, and Greenwood and Bradshaw[22] compared the same two doses of temazepam with oxazepam for premedication in outpatient anesthesia; both groups found temazepam was a superior anxiolytic and sedative compared with placebo or oxazepam.

Most of the studies reporting superior effects of temazepam as a premedicant came from Europe, where the drug is available in a solution and in a soft gelatin capsule. In the United States, temazepam is only available in hard capsule form, which is not particularly useful for the purpose of premedication because in this form the onset of action of the drug is delayed and the duration of action is prolonged.

TRIAZOLAM (Halcion, Upjohn)

Triazolam, a new triazolo benzodiazepine hypnotic (see Fig. 1), differs greatly from temazepam in its pharmacokinetic properties (see Table 1). Following oral administration, approximately 85 per cent of a dose is absorbed, and peak plasma concentrations are obtained 0.7 to 2 hours after ingestion.[14] When the pH is lower than 4, triazolam undergoes rapid, reversible acid hydrolysis and cleavage of the azomethine bond to form an open-ring inactive structure. At a pH greater than 5, triazolam exists primarily in the closed-ring active form. Environmental pH determines the relative amounts of the two forms. The lower the pH, the higher the concentration of the open-ring form. If absorbed in the open-ring form, metabolism can occur directly. This reduces the systemic availability of triazolam.[28] In a recent study, Scavone and associates[44] evaluated the pharmacokinetic properties of triazolam after sublingual administration and found that the total area under the plasma concentration curve was significantly larger following sublingual compared with oral administration. Elimination of the first-pass effect by sublingual administration may have resulted in the 28 per cent increase in triazolam bioavailability. Peak plasma concentration, time of peak concentration, and elimination half-life were not significantly different between sublingual and oral administration. Absorption half-life is reported to range from 2.8 to 8 minutes.[14] Food reduces the rate of absorption of oral triazolam.

Triazolam's volume of distribution ranges from 0.8 to 1.3 L per kg and is not changed significantly in obese persons compared with individuals with normal body weight. Oral clearance, however, is significantly lower in obese subjects receiving triazolam compared with patients of normal body weight (340 vs. 531 ml per min).[1] Triazolam is 89 to 94 per cent bound to plasma proteins, and plasma protein binding is unchanged in obese patients.[1,34] Triazolam's binding ratio (bound:unbound concentrations) correlates with acid glycoprotein concentration but not with albumin concentration, age, or sex. As acid glycoprotein concentration rises, the free triazolam fraction decreases. Triazolam differs from other benzodiazepines by an insignificant binding affinity for serum albumin. It is postulated that the triazolo ring impairs binding to albumin.[29]

Triazolam is metabolized in the liver by hydroxylation followed by glucuronide conjugation. The major metabolite is α-hydroxytriazolam, which retains 50 to 100 per cent of the pharmacologic activity of the parent drug and has an elimination half-life of approximately 4 hours. This metabolite is not likely to be of clinical importance, however, because it is present in the plasma in very small amounts, primarily in the inactive, conjugated form.[14,34] The elimination half-life of triazolam ranged from 1.4 to 3.9 hours, with a mean of 2.4 hours. Elimination half-life is prolonged in obese patients compared with persons of normal body weight (4.1 vs. 2.6 hr).[1] Dehlin and coworkers[10] reported no evidence of accumulation or changes in pharmacokinetic parameters in the multiple dosing of triazolam in geriatric patients.

Cimetidine interacts with benzodiazepines that are metabolized by hydroxylation or n-dealkylation, resulting in their delayed clearance and increased pharmacologic effects such as sedation. Triazolam given concomitantly with cimetidine resulted in a significant increase in the plasma elimination half-life of triazolam as well as in reduced clearance of the drug.[43] This finding may be important in patients who are predisposed to toxicity, such as the elderly, patients with hepatocellular disease, and patients concurrently receiving other sedatives.

Erythromycin inhibits the metabolism of triazolam, leading to an exaggerated pharmacologic response. Concomitant administration of triazolam and erythromycin resulted in significant decreases in triazolam clearance and increases in triazolam serum concentrations. The elimination half-life of triazolam was significantly prolonged.[40]

Renal disease does not affect triazolam elimination. Triazolam can, therefore, be used in normal doses in patients with renal dysfunction.[28]

TRIAZOLAM AS A PREMEDICANT

With a short half-life of 2.4 hours, triazolam has been extensively used as a hypnotic but so far has received little attention as a premedicant.

Pinnock and colleagues,[42] in a randomized double-blind trial with 90 patients undergoing minor gynecologic surgery, compared triazolam 0.25 mg with diazepam 10 mg and a placebo as premedicants. All medications were given orally, approximately 2 hours prior to anesthesia and immediately after baseline assessment. Both triazolam and diazepam produced a significant sedative effect as measured by patient self-assessment and linear analogue scales. There was little difference in sedative properties between the two drugs used as premedication. In the doses used, triazolam produced less preoperative anxiolysis but created greater impairment of psychomotor performance at 3 hours after awakening than diazepam. Triazolam was shown to have a pronounced amnesic effect in comparison with the placebo. It was concluded from this study that triazolam 0.25 mg orally is a sedative hypnotic devoid of anxiolysis. Pinnock and colleagues[42] presumed that triazolam had limited use for premedication and was indicated for use only when hypnosis in association with a strong amnesic effect was required.

Thomas and co-workers[54] conducted a randomized, double-blind study with 58 female patients undergoing laparoscopy, comparing triazolam 0.25 mg with lorazepam 2 mg or a placebo as oral premedication. Triazolam and lorazepam caused a significant anxiolytic effect compared with the placebo. Sixty minutes after premedication, patients who had received triazolam were sleepier than patients given lorazepam or the placebo. At 6 hours after the operation there was no difference between triazolam and the placebo, but patients who had received lorazepam were significantly more sleepy than those given the placebo. It was concluded the triazolam 0.25 mg orally produced effective preoperative anxiolysis and sedation; recovery occurred within 6 hours after surgery.

Ziegler and associates[57] compared intravenous midazolam with intravenous triazolam given in a formulation containing glycofurol as a solvent. Sedation, rated by investigator assessment, tracing tests, reaction tests, memory tests, and patients' self-assessment, was found to be less intense with triazolam 0.25 mg; however, the duration of effect (5 hr) was similar to midazolam 15 mg. In all tests performed, the maximum effect of 15 mg midazolam was greater than that of 0.25 mg triazolam. The findings seem to indicate that triazolam 0.25 mg has a mild and short-acting effect. In higher doses (1 mg) the sedative effect of triazolam is extremely rapid, more intense, and longer lasting than midazolam 15 mg (10 hr vs. 5 hr). Currently, the parenteral form of triazolam is not commercially available in the United States.

Baughman and co-workers[5] compared three doses of oral triazolam (0.125, 0.25, and 0.5 mg) with three doses of oral diazepam (5, 10, and 15 mg) and a placebo as premedicants. A nurse-clinician made all the observations. The authors concluded that all doses of triazolam and the two higher doses of diazepam were significantly better than the placebo in terms of hypnotic effect and anxiolysis. The highest dose of triazolam also produced significant anterograde amnesia. Stallworth and colleagues[51] performed a similar study comparing triazolam 0.5 mg with diazepam 10 mg, both given orally. Both drugs produced significant sedation compared to the placebo. Patients receiving triazolam were found to be excessively sedated both before and after operation. Neither diazepam nor triazolam was a better anxiolytic than the placebo.

Thus it appears that, in spite of its short elimination half-life, the effect of triazolam as a premedicant is somewhat unpredictable and sometimes depresses the central nervous system too much. At times this depressant action extends well into the postoperative period, complicating the recovery phase. More research is indicated, possibly with smaller doses, and with either sublingual or intravenous administration.

NEW NARCOTIC DRUGS AS PREMEDICANTS

The uses of the newer narcotic analgesics during and after operations have been discussed in the article by Dr. Rosow in this issue. However, some of the new synthetic narcotics like fentanyl and sufentanil were shown to be useful as intravenous premedicants in outpatient surgery. Pandit and Kothary[36] compared small doses of fentanyl, sufentanil, morphine, and meperidine with placebo as intravenous premedicants in healthy outpatients scheduled for laparoscopic procedures. Compared with placebo, sufentanil and to a lesser extent fentanyl produced significant anxiolysis in these patients and improved the quality of induction and maintenance of anesthesia without increasing postoperative side effects or prolonging discharge times.

The agonist-antagonists have also been used as premedicants. Reports of bizarre central nervous system disturbances soon followed the introduction of pentazocine in 1967. Hallucinations were the most frequently reported side effects. Efforts to minimize the psychotomimetic effects of pentazocine led to the synthesis of four new agonist-antagonists in the last 5 years. These are butorphanol, nalbuphine, buprenorphine, and dezocine. Pharmacokinetic parameters of some of these drugs are shown in Table 2. All four drugs are potent analgesics and have excellent sedative properties.

Laffey and Kay[30] compared butorphanol 2 mg intramuscularly with morphine 10 mg intramuscularly as premedicants in 40 women undergoing abdominal hysterectomy. Morphine produced dizziness

Table 2. *Pharmacokinetic Data for New Opioid Agonist-Antagonists*

PARAMETER	BUTORPHANOL	NALBUPHINE	BUPRENORPHINE
Onset of action (min)	10 (IM)	15 (IM) 2–3 (IV)	15 (IM)
Peak effect (min)	30–60	60 (IM)	60 (IM)
Duration of action (h)	3–4	3–6	6–7
Elimination half-life (h)	2.5–3.5	5.0	2–3
Percent excreted unchanged in urine	5	7	Negligible

*IM = intramuscular; IV = intravenous

and pain on injection more frequently than butorphanol. A statistically significant number of patients given butorphanol reported a flushed feeling more often that those given morphine. Analgesia produced with the drugs was comparable; however, patients treated with butorphanol required postoperative analgesic significantly earlier than patients who received morphine. Others have demonstrated that the preoperative analgesia produced by butorphanol is comparable to that of morphine; the side effects reported were also similar. Thus, butorphanol does not appear to offer significant advantages over morphine as a premedicant and is more expensive than morphine.

Pinnock and associates[41] compared nalbuphine 10 mg with morphine 10 mg as premedicants in a randomized double-blind trial with 50 patients undergoing gynecologic surgery. Both drugs were given intramuscularly one hour prior to anesthesia. Sedation produced by the two drugs was comparable, and neither drug produced anxiolysis as assessed by linear analogue scales and observation assessments. Nalbuphine produced calm and sedated patients more frequently and to a greater extent than morphine, but the differences were not statistically significant. Adverse effects were similar.

In a study of 129 patients undergoing gynecologic surgery, Sear and co-workers[46] compared buprenorphine with papavaretum as premedicants. Drowsiness and tranquility were greater among patients given buprenorphine, compared with the group receiving papavaretum. The analgesia produced was similar in degree and duration with both drugs. In a previous trial comparing buprenorphine 0.3 mg intramuscularly with morphine sulfate 10 mg intramuscularly as premedicants, Sear and associates[47] reported that buprenorphine was more soporific and had a longer duration of action than morphine, but the frequency of side effects was also greater with buprenorphine.

Dezocine (Wyeth), a new and not yet approved agonist-antagonist type of analgesic, may have some advantages over other drugs in the same category because of its quicker onset and short duration of effect. Unlike pentazocine, nalbuphine, and butorphanol, dezocine has minimal or no effect on kappa and sigma receptors, making it less likely to cause psychotomimetic side effects. Although dezocine has not been used for premedication, its sedative properties have been observed.[37,38] Dezocine may be useful as a premedicant in certain special situations in which analgesia may be necessary.

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What's New in Drugs Used in Obstetrics?

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Relatively few new drugs have been introduced in recent years for obstetric practice. Therefore, this article will mainly discuss the current thinking on established drugs and techniques for obstetric anesthesia. Included will be information about anesthesia for vaginal delivery and cesarean section, pain control during labor and postpartum, and new drugs that obstetricians are using that may interact with anesthetic agents.

Patient-controlled analgesia and epidurally administered opioids are recent forms of postoperative pain control often used after cesarean section. Patient-controlled analgesia provides better pain control with lower maternal blood levels of the opioid used and a lower drug dose than traditional modes of analgesic administration. This method provides a relatively stable level of analgesia and reduces the time commitment of the anesthesiologist. Epidurally administered opioids given alone produce poor relief of labor pain but are highly effective to treat post-cesarean section pain. Although late respiratory depression and other troublesome side effects limit the wider application of these techniques, they have been relatively safe in obstetric anesthesia practice.

To prevent the serious complication of Mendelsohn's syndrome, particulate or colloidal antacids have generally been replaced by a clear, nonparticulate antacid (sodium citrate) administered shortly before induction of general anesthesia. Metaclopramide is recommended to increase gastric emptying and to raise the gastroesophageal sphincter tone. Histamine H_2 receptor anatagonists are also recommended before general anesthesia and, to a lesser extent, intermittently during labor to prevent further production of gastric acid.

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Prostaglandins of the E and F series are used by obstetricians, other than as abortifacients, to shorten induced labors and control postpartum hemorrhage. Although ritodrine is still the standard drug for treatment of premature labor, the safety of beta-sympathomimetic therapy is still questioned. Therefore, there is renewed use of magnesium sulfate as a uterine tocolytic while other agents (for example, indo-methacin, nefedipine) are under investigation as possible tocolytics.

SYSTEMIC MEDICATION

Mode of Administration

Pharmacokinetically, fetal blood levels of drugs will usually parallel maternal drug levels. Fetal blood levels of the highly lipid soluble narcotic agents can exceed maternal blood levels.[100,106] Intramuscular administration of opioids for labor analgesia produces variable and unpredictable blood levels[7] and a delayed analgesic effect. Absorption of opioids from intramuscular sites can be enhanced by vasodilatation from autonomic blockade after regional anesthesia and marked maternal drowsiness and stupor may occur. The intravenous route, therefore, produces better controlled and more predictable maternal analgesia. This results in less maternal sedation because a lower total dose is required. Incremental doses of intravenous drugs should be injected at the start of uterine contractions because higher fetal drug levels occur if drugs are administered between contractions.[100] Uterine blood flow is blocked by myometrial contraction, and by the time uteroplacental blood flow is restored, maternal drug levels decrease so there is a lower diffusion gradient across the placenta.

Narcotic Analgesics

Alphaprodine was recently withdrawn from the United States market for economic reasons. Meperidine, the most commonly used opioid for labor analgesia, may be less than ideal for labor management because of its potent metabolite, normeperidine,[77] its propensity to cause nausea and vomiting, and its vagolytic effect, producing maternal tachycardia.[58] This has caused alternative narcotic agents to be examined for the parturient. The newer opioids may have theoretical advantages for the parturient, but, unfortunately, few studies have adequately evaluated their effect on the mother and neonate. This has resulted in the reintroduction of morphine, hydromorphone, and oxymorphine for labor analgesia.

Of these three drugs morphine is the most commonly studied in obstetric patients. It is not ideal for the parturient because of its long duration of action (approximately 4 to 6 hours), its slow onset of activity (about 20 minutes) after intravenous administration, and its production of more neonatal depression[119] when compared with equipotent doses of meperidine. It is mainly used as the agent of choice to produce sleep in the parturient who may be in the prolonged latent phase of labor or in false labor.

Hydromorphone is used at Northwestern University's Prentice Women's Hospital as an alternative to meperdine because it appears to cause less nausea and vomiting. Hydromorphone, 1.0 mg, both intravenously and intramuscularly, provides the parturient approximately 1½ hours of pain relief; considerably less than that reported for hydromorphone in nonpregnant patients.[56]

Oxymorphone, ten times more potent than morphine and with a faster onset, was suggested as another alternative opioid. It produces few cardiovascular effects and no histamine release.[33] Although its duration of activity in the pregnant patient is unreported, it may last as long as morphine. These properties may make it preferable to morphine for a laboring patient with severe cardiac disease.

Agonist-antagonist analgesics may be useful for pain control. With an elimination half-life of 2.7 hours and no active metabolites,[102] butorphanol would seem pharmacokinetically suited for the obstetric patient. Comparative pharmacodynamic studies of butorphanol (1 to 2 mg) and meperidine (40 to 80 mg) show that butorphanol is as effective as meperidine in relieving labor pain, causes less nausea and vomiting, and has similar effects on the newborn.[50,70] However, butorphanol tends to produce drowsiness, which limits its usefulness in obstetrics.

Nalbuphine is another agonist-antagonist analgesic that is chemically related to naloxone and oxymorphone. Nalbuphine has few cardiovascular effects, causes little nausea and vomiting, and there is a ceiling effect on respiratory depression.[91] This ceiling effect on respiratory depression would be advantageous for the parturient when nalbuphine is given by bolus injection to the parturient. Nalbuphine had an elimination half-life of 2.4 hours in the parturient.[121] No studies are reported that compare nalbuphine with other narcotic agents in laboring patients. However, one study compares nalbuphine given by intermittent intravenous injection with that given by patient-controlled analgesia (PCA) for the control of labor pain. There was a lower total dose of nalbuphine required for analgesia, less use of antiemetics, and more satisfaction with the method of analgesia in the group treated with the PCA system.[87] There were no differences in fetal effects between the two groups as judged by fetal monitoring records and Apgar scores at delivery.

Sufentanil and alfentanil are recently introduced derivatives of fentanyl. There are few studies of the short-acting narcotic analgesics fentanyl and sufentanil and the ultra short-acting alfentanil in laboring patients. Fentanyl has little effect on the neonate when given within 10 minutes of delivery.[30] When used as a primary labor analgesic, fentanyl 50 μg intravenously and 100 μg intramuscularly provides pain relief for approximately 1 hour. This short duration of action, coupled with an obstetric guideline that patients must be reexamined before being remedicated, limits its usefulness. The rapid onset of effect of fentanyl and its derivatives makes them good agents for giving prompt relief to patients who have a sudden need for more analgesic. All of these agents have few cardiovascular effects and theoretically they may be anesthetic induction agents of choice in a parturient with severe cardiac disease. However, induction doses of these opioids could severely depress the fetus. Which of the three would have the least effect on the neonate is currently unknown. Theoretically, the shorter half-life and a smaller volume of distribution of alfentanil would make it superior to fentanyl and sufentanil, but comparative studies are needed to identify the better agent, if any of them would be useful in such circumstances.

Benzodiazepines

The benzodiazepines, particularly diazepam, were widely used as supplements to the opioids in the first and second stages of labor. However, their use in obstetrics is still controversial because they cause neonatal respiratory depression. Diazepam is a poor choice as an antepartum agent because of its long half-life,[76] its active metabolite N-desmethyldiazepam,[99] and its propensity to produce neonatal respiratory depression, hypothermia, muscular relaxation, and limpness.[26,93,103] These effects on the newborn, however, may be related to excessive (>30 mg) or repetitive use of diazepam[61] and can be minimized if diazepam is given intravenously at the beginning of a uterine contraction.[46]

Newer benzodiazepines, oxazepam, lorazepam, and midazolam, have shorter half-lives than does diazepam, no active metabolites, and may offer the parturient an alternative anxiolytic agent antepartum and intrapartum. These benzodiazepines may decrease the need for narcotic analgesics.

Oxazepam (25 mg orally) was rapidly absorbed in the parturient with similar peak plasma concentrations and area under the curve measurements as nonpregnant patients. Maternal plasma elimination half-life was 5 to 8 hours, shorter than that reported for nonpregnant patients. Although studied in a small number of patients, oxazepam is the only benzodiazepine that causes no adverse effects in the newborn,[112] but it is only available as an oral agent, which limits its obstetric use. The neonatal plasma elimination half-life was three to four times longer than the maternal half-life.

There is one report on the use of lorazepam in obstetric anesthesia. A double blind study with a placebo control demonstrated that lorazepam (2 mg) helps relieve labor pain and increases patient satisfaction.[74] Lorazepam did produce undesired maternal amnesia for labor events. Although neonatal respiratory depression occurred with lorazepam, no differences in Apgar scores and neonatal neurobehavioral assessment were found between the two groups.

Midazolam, the newest injectable benzodiazepine, has an elimination half-life of 0.5 to 2.0 hours in the parturient,[60] shorter than that reported for nonpregnant patients. Its rapid onset of effect and short elimination half-life appear to make it a better choice for obstetric use than the older benzodiazepines. However, neonatal respiratory depression occurred more frequently after midazolam in a comparative study of thiopental (3.5 mg per kg) and midazolam (0.2 mg per kg) administered by rapid sequence for induction of anesthesia for cesarean section.[15] Unfortunately, antegrade amnesia produced by midazolam, 2 to 7 mg intravenously, can deprive mothers of the memory of the birth experience[19] when regional anesthesia is used, but the amnesic action of midazolam may also be beneficial during cesarean section where maternal awareness under light general anesthesia can be a problem.[83,96] When hemodynamic stability is essential, such as severe preeclampsia, midazolam may be used as an alternative induction agent because it was reported to promote maternal cardiovascular stability and maintain placental perfusion.[15]

PATIENT-CONTROLLED ANALGESIA

PCA is not a new innovation in obstetric analgesia. In 1970 parturients used a hand-held clamp to control the intravenous infusion of meperidine.[98] Today there are a number of special programmable infusion pumps (Abbott Life Care PCA, Bard Harvard PCA, Graseby Cardiff Palliator, and Pharmacia Prominject) that are relatively simple to operate, deliver a predetermined dose of medication (the increment) on patient demand, and limit patient access to the medication (lockout time). A loading dose is usually administered to relieve acute pain and to demonstrate analgesic effectiveness.

A number of drugs have been used by PCA. Meperidine administered in increments of 0.25 mg per kg required a mean total dose of 2.2 mg per kg for the first stage of labor.[32] This dose provided similar analgesia to the standard single 150 mg dose of intramuscular meperidine to which it was compared. In another study, meperidine administered by PCA was compared with the traditional intramuscular injection of meperidine and resulted in as good, if not better, analgesia from a smaller total dose of meperidine.[90] In a third study, PCA resulted in good analgesia with 20 per cent less drug used compared with a continuous infusion of meperidine.[10]

Nalbuphine is as effective as morphine[38] and meperidine[8,104] when administered by PCA for postoperative pain relief. PCA administration of nalbuphine (3 mg increments) compared with meperdine (15 mg increments) with a lockout time of 10 minutes resulted in better labor pain relief with nalbuphine.[73] There were no significant differences in Apgar scores, time to sustained respiration, or neurobehavioral assessment of the neonates. When nalbuphine administered by PCA was compared with intermittent intravenous injections for labor pain relief, the PCA patients required about a third less nalbuphine, had a 5 per cent versus 53 per cent incidence of side effects requiring treatment, and expressed greater satisfaction with the treatment compared with the control patients.[87]

Oxymorphone (0.3 mg increment) and meperidine (18 mg increment) provided excellent analgesia and higher patient satisfaction than did morphine (1.8 mg increment) PCA with an 8 minute lockout time when used for postcesarean pain relief.[47] Fentanyl administered by intravenous PCA demonstrated no obvious clinical benefits over epidural PCA although the onset of analgesia was more rapid with the intravenous route.[31]

PCA is now a well-accepted technique for the treatment of postoperative pain. While there are a limited number of studies in obstetric patients, PCA is an effective mode of opioid administration for the laboring patient. However, the PCA system must be properly set up to avoid potentially life-threatening complications that can result from opioid overdose.[120]

EPIDURAL ANALGESIA

While epidural analgesia is the most effective method for the relief of pain during labor and delivery, it inhibits uterine contractions, especially in early labor, and results in a higher incidence of malpositions and forcep deliveries. The addition of epinephrine (1 to 200,000) to caudal anesthetics prolongs labor and increases the need for oxytocin augmentation of labor.[43] Several investigators recommend that patients receiving epidural analgesia be permitted a longer second stage of labor and delay "pushing" to minimize the need for an instrumented delivery.[9,71,86] Thus, the goal of epidural anesthesia should be fast and reliable pain relief for active painful labor and for delivery without slowing early labor and interfering with "pushing."

Intermittent Epidural Injection

The choice of local anesthetics can be tailored to patient needs more easily when epidural analgesia is administered in early labor. There are wide variations in patient response to a given drug and repeated administration of intermediate and long duration local anesthetics (especially bupivacaine, 0.25 to 0.5 per cent) may be associated with a more profound motor block. The availability of short duration (chloroprocaine), intermediate duration (lidocaine, mepivacaine), and long duration (bupivacaine) local anesthetics in varying concentrations or in combination (lidocaine and bupivacaine) possibly with the addition of epinephrine and/or narcotics provides greater fexibility to tailor anesthetic effect to patient desires and labor progress. Epidural fentanyl (50 to 100 μg) and to a lesser extent butorphanol (1 to 2 mg) and sufentanil (20 to 40 μg) alone or in combination with weak concentrations of bupivacaine (0.0625 to 0.125 to 0.25 per cent) are administered in early labor and in the second stage of labor to facilitate maternal pushing and expulsive efforts.[85,118]

Epidural fentanyl (50 to 100 μg) diluted with preservative-free saline to 10 to 15 ml provides more effective and longer duration analgesia in very early labor than systemic fentanyl. The addition of small amounts of bupivacaine (10 to 15 mg) markedly potentiates the effectiveness of epidural fentanyl.[45] Patients in early labor may receive adequate pain relief with 10 to 12 ml of epidural fentanyl (50 μg) combined with bupivacaine 0.125 per cent ± epinephrine 1 to

300,000. If analgesia is inadequate in 30 minutes, the dose should be repeated. Subsequent doses may be adequate or stronger medication may be required for more active labor with a return to this formulation or just epidural fentanyl during the second stage of labor to minimize the effect on pushing.

The active primigravida (5 to 6 cm dilation) may receive for the initial dose either bupivacaine 0.25 per cent ± epinephrine ± fentanyl or a mixture of bupivacaine and lidocaine ± epinephrine for the initial dose. Bupivacaine 0.25 per cent ± epinephrine 1 to 300,000 ± fentanyl 50 μg, 10 to 12 ml, may have a slow onset time (20 to 30 minutes) and a short duration of effect (75 to 90 minutes) but the second dose should last 90 to 150 minutes. Both epinephrine and fentanyl increase the duration of epidural bupivacaine 0.25 per cent.[22,42] A 50/50 mixture of bupivacaine 0.5 per cent and lidocaine 1.0 per cent (final concentration bupivacaine 0.25 per cent and lidocaine 0.5 per cent) with epinephrine 1 to 300,000 (10 to 12 ml) for labor and 12 to 15 ml for perineal anesthesia, provides fast, reliable analgesia of 2 to 3 hours duration. Usually perineal analgesia is obtained with the second labor dose. Repeat administration of either bupivacaine 0.25 per cent or the mixture of bupivacaine and lidocaine may cause significant motor block requiring the anesthesiologist to administer a weaker local anesthetic concentration for subsequent doses.

The active multiparous patient may receive lidocaine or mepivacaine for the first epidural dose. Lidocaine 1.0 per cent with epinephrine 1 to 300,000 or mepivacaine (plain), 8 to 10 ml, provides fast, reliable analgesia lasting 75 to 90 minutes. A 12 to 15 ml injection, preferably administered through an epidural needle in the sitting position, provides rapid perineal anesthesia. The intermediate duration of analgesia permits patient stabilization in the labor room before their transport to the delivery room. If more than 2 to 3 labor doses are anticipated, a longer acting agent should be substituted because the intermediate acting drugs exhibit tachyphylaxis, shorter durations of action on repeat administration.

Bupivacaine 0.375 to 0.5 per cent ± epinephrine 1 to 300,000, 6 to 10 ml, is not as desirable a drug for labor epidurals because the first dose may have a relatively slow onset and short duration of effect in active labor. Repeat administration may result in both long lasting motor block and analgesia. Because it is difficult to tailor the anesthetic effect to labor progress with this concentration of bupivacaine, obstetricians may prefer that the block wears off even before the second stage of labor.

Chloroprocaine is unique among local anesthetics because it does not cause systemic toxicity after repeated doses due to its rapid enzymatic degradation.[66] It is the drug of choice for certain high-risk patients (placental insufficiency, prematurity) to test catheter placement or for fast, short duration perineal anesthesia in the delivery room. Chloroprocaine 2 per cent, 6 to 10 ml for labor and 10 to 15 ml for perineal anesthesia, produces a rapid onset of effect, reliable analgesia, and short duration of action (40 to 60 minutes) without tachyphylaxis but it does cause a significant motor block of short duration. Chloroprocaine 3 per cent, (10 to 12 ml) provides faster and stronger perineal anesthesia to facilitate forceps delivery.

Continuous Epidural Infusion

The continuous infusion of local anesthetics through the epidural catheter during labor was first described in 1963,[97] but the technique gained popularity only after the advent of a reliable infusion device. Procaine,[53] chloroprocaine,[62] lidocaine,[122] and bupivacaine[39,108] in various concentrations and flow rates, have been studied. Generally, weaker solutions (chloroprocaine 0.75 per cent, lidocaine 0.4 per cent, and bupivacaine 0.125 per cent) with greater flow rates (10 to 25 ml per hour) have been more successful than stronger solutions. The technique provides a relatively stable level of analgesia avoiding the "roller coaster" effect of intermittent injections, although it is less reliable for the second stage of labor. Another purported advantage is the need for less manpower so that more patients can receive the benefits of epidural anesthesia on a busy obstetric service. However, continuous epidural anesthesia should be conducted with the same precautions that are used with intermittent injections. Even when a satisfactory and stable block is obtained, the patient should be evaluated at least once an hour for the adequacy of pain relief and level of anesthesia. The infusion rate should be decreased if the level ascends or increased (following a bolus injection) if it descends. More importantly, the epidural catheter may migrate into a blood vessel or into the intrathecal space. A typical epidural infusion of bupivacaine (0.125 per cent at 10 ml per hour) would result in a 12.5 mg subarachnoid dose over 1 hour. In one report, the sensory block slowly increased to T_4 with a gradual increase in lower extremity motor block.[45,72] An intravascular catheter migration would deliver about 0.2 mg per kg per hour systemically so that loss of analgesia would occur long before any signs or symptoms of systemic toxicity. However, if the catheter migrated into either of these unwanted areas, drug administered by infusion would result in less toxicity than if large bolus injections were made through the catheter.

The use of dilute solutions of local anesthetics for continuous infusion may result in a less intense motor block. Maintaining a continuous epidural infusion of bupivacaine 0.125 per cent during the second stage of labor may prolong the second stage and increase the frequency of instrumented deliveries in nulliparous women.[21] There are several reports on the continuous infusion of bupivacaine compared with bupivacaine combined with fentanyl. Sherman et al[101] reported better pain relief with bupivacaine 0.125 per cent combined with fentanyl 2.5 μg per ml compared with an infusion of bupivacaine 0.125 per cent alone. Chestnut et al[20] reported similar pain scores and a less intense motor block, which neither resulted in a shorter second stage nor a greater frequency of spontaneous delivery when bupivacaine 0.0625 per cent with fentanyl 2.0 μg per ml was compared with an infusion of bupivacaine 0.125 per cent alone.

CESAREAN SECTION

Hyperbaric bupivacaine, 0.75 per cent for spinal anesthesia is the only "new" local anesthetic in obstetric anesthesia practice. Its use for cesarean section is increasing. Bupivacaine 0.75 per cent is no longer recommended for epidural use because of its cardiotoxicity in the obstetric patient.[34] Bupivacaine 0.5 per cent is commonly used for cesarean section although chloroprocaine 3 per cent and lidocaine 1.5 to 2.0 per cent are regaining their popularity, despite earlier concerns about neurotoxicity (chloroprocaine) and neurobehavioral changes (lidocaine and mepivacaine). Bupivacaine should be administered slowly and incrementally after a suitable test dose because 44 maternal cardiac arrests (0.75 per cent, 31; 0.5 per cent, 12; 0.25 per cent, 1) with 30 deaths are reported since its introduction in the United States in 1973.[6] Neurotoxicity for unintentional intrathecal injection of chloroprocaine is less likely to occur since the availability of chloroprocaine with a reduced sodium metabisulfite concentration (0.2 per cent reduced to 0.07 per cent). More recently, a metabisulfite-free formulation became available.[2] Long-term adverse effects have not been demonstrated in association with impaired neurobehavior assessment first described by Scanlon et al[95] in 1974 following epidural anesthesia with lidocaine or mepivacaine.

Regional Anesthesia

Spinal anesthesia for cesarean section is regaining popularity at academic centers because opioids (morphine 0.1 to 0.5 mg added to the local anesthetic[1,3]) can be safely added to the local anesthetic and because a more reliable and longer acting spinal anesthetic agent (hyperbaric spinal bupivacaine 0.75 per cent) or combination of agents (tetracaine 1.0 per cent with hyperbaric procaine 10 per cent, tetracaine 1.0 per cent with hyperbaric lidocaine 5.0 per cent) are available. The quality of epidural anesthesia for cesarean section can be improved by adding fentanyl (50 to 100 μg) to the local anesthetic solution initially[89] or administering it immediately after delivery.[65] The intravenous or epidural administration of fentanyl, 1.0 μg per kg, prior to cesarean section was neither associated with adverse neonatal effects nor late maternal respiratory depression.[30,67,89] Another method to improve the quality of epidural anesthesia for cesarean section is the addition of tetracaine 10 to 30 mg to 20 ml of lidocaine 1.5 to 2.0 per cent.

Intraspinal Opioids

Epidurally administered opioids produce disappointing relief of labor pain but are highly effective for relief of postcesarean section pain. Morphine (3.5 to 5.0 mg), hydromorphone (0.75 to 1.25 mg), meperidine (50 to 75 mg), butorphanol (2 to 4 mg), fentanyl (50 to 100 μg), sufentanil (20 to 50 μg), and continuous infusion of fentanyl, sufentanil, or alfentanil have all been effective. A combination of fentanyl (50 to 100 μg) and morphine (3.5 to 4.0 mg) provides both a rapid onset and long duration of pain relief after cesarean section.[65] Intrathecally administered opioids have a limited role in labor analgesia (morphine 0.5 to 1.0 mg in patients with severe cardiopulmonary dysfunction[5,54]) but are equally as effective at 1/10 (or less) of the epidural dose for post surgical pain relief. Intrathecally administered fentanyl (6.25 to 50 μg) provides 2 to 4 hours of pain relief postcesarean section.[52] Late respiratory depression[44] with the longer-acting agents (morphine, hydromorphone, meperidine) is extremely rare in obstetric patients. However, concern for its occurrence and the more common side effects of nausea and pruritis, which may be troublesome in a few patients, limit the wider acceptance of these techniques. Late respiratory depression has not been reported after epidural administration of fentanyl, sufentanil, or butorphanol. However, epidural catheter placement should be tested for intrathecal migration before repeat injection of longer acting opioids to avoid sudden respiratory depression.[17] Naloxone, 0.1 to 0.2 mg intravenously or by continuous infusion, is usually effective in controlling side effects. Recently, nalbuphine (5 to 10 mg intravenously) was recommended for the treatment of pruritis and break-through pain.[84] Alternatively, epidurally administered butorphanol, 3 to 4 mg, provides 6 to 8 hours of pain relief postcesarean section, without causing pruritis. A few patients may complain about drowsiness but butorphanol is well accepted by most patients.

General Anesthesia

Thiopental, ketamine (in the presence of hypovolemia), and etomidate (for cardiovascular instability when ketamine is not appropriate) are most commonly used to induce general anesthesia for cesarean section. Blood pressure and heart rate response to either thiopental or ketamine given alone can be blunted by the administration of ketamine (0.75 mg per kg) followed by thiopental (1.0 mg per kg).[96] Propofol, a new intravenous anesthetic agent, was used as an anesthetic induction agent (2.5 mg per kg) for cesarean section in healthy patients without the occurrence of any adverse maternal or fetal effects.[27] A "cardiac-type" induction with high-dose fentanyl (valvular lesions, 20 to 30 μg per kg; myocardial ischemia, 50 to 75 μg/kg) or sufentanil is recommended for patients with severe cardiopulmonary dysfunction.

Volatile anesthetics in equipotent concentrations have similar effects on uterine tone (and uterine bleeding) and fetal depression. When halothane 0.5 per cent, isoflurane 0.75 per cent, or enflurane 1.0 per cent are used for cesarean section, they prevent maternal awareness.

The shorter acting nondepolarizing muscle relaxants, atracurium and vecuronium, are now commonly used following succinylcholine for cesarean section or postpartum tubal ligation. When succinylcholine is contraindicated, rapid endotracheal intubation may be facilitated by using a "priming" dose (0.01 mg per kg) followed 4 to 6 minutes later by an "intubating" dose (0.1 mg per ml) of vecuronium.[109] The priming dose may produce a profound neuromuscular block in particularly sensitive patients and could be potentially dangerous if not recognized.

The routine use of antacids to prevent pulmonary aspiration of acid gastric contents is controversial. Studies show a wide variation in the duration of protection afforded by prophylactic antacid use,[81] and some antacids may cause a chemical pneumonitis.[38] Moreover, studies of maternal mortality in the United Kingdom show that maternal deaths occurred due to aspiration pneumonitis despite antacid therapy.[110,111] Although controversial, repetitive administration of particulate or colloidal antacids during labor has generally been replaced by clear, nonparticulate antacids (sodium citrate) administered shortly before induction of general anesthesia. The H_2-receptor antagonists, cimetidine or ranitidine, effectively reduce gastric acidity and gastric volume[23,117] by blocking the production of gastric secretion. They increase gastric pH above 2.5, 60 to 90 minutes after administration. Ranitidine is preferable to cimetidine because it does not inhibit hepatic oxidative drug metabolism.[64] Additionally, ranitidine has a longer duration of action and it directly increases lower esophageal tone.[14] Metaclopromide is a hyperkinetic agent that accelerates gastric emptying during labor[51] and increases lower esophageal tone.[16] When it is given with H_2 blockers, maximum protection from gastric aspiration may result.[88] Even though more than 10,000 parturients received these drugs without any detectable adverse maternal or neonatal effects,[75] many anesthesiologists do not routinely administer H_2-receptor antagonists.

UTERINE ACTIVE AGENTS

Oxytocics are used to stimulate labor and improve the quality of uterine contractions. In a novel and more physiologic approach to labor induction with oxytocin, it was "pulsed" 1 minute in every 10-minute period,[82] mimicing the natural pulsatile spurts during parturition.[28,37] When compared with the standard oxytocin regimen, there was no clinical difference in induction to delivery time, but the total dose of oxytocin was significantly less in the group administered oxytocin in a pulsatile manner. This dose reduction matters little in the mother, but the incidence of neonatal hyperbilirubinemia, associated with oxytocin infusion rates greater than 20 mU per minute would be less.[59]

The E and F series prostaglandins, considered locally active hormones, are used as abortifacients in obstetrics. They rarely cause life-threatening maternal adverse effects.[55] However, their use is associated with uncomfortable side effects on the gastrointestinal tract, primarily causing nausea, vomiting, and diarrhea, and on the thermoregulatory center in the hypothalamus, producing pyrexia.[116] Their most significant cardiovascular effect is the ability to alter blood pressure. Prostaglandin E_2 is a potent vasodilator and is generally safe to use in the severely hypertensive patient, but it can produce extreme hypotension, particularly in a patient with decreased intravascular volume. Prostaglandin F_2 alpha, in contrast, predominantly causes vasoconstriction. It can precipitate a hypertensive crisis in the preeclamptic patient and should be avoided in patients with hypertensive disorders of pregnancy. Obstetricians use them for cervical ripening and to control postpartum hemorrhage.

Prostaglandin E_2 produces biochemical changes in the connective tissue matrix of the cervix prior to parturition.[69] Various investigators in small clinical trials used prostaglandin E_2 suspended in a vaginal gel or formulated as a vaginal suppository and found that 2 to 5 mg doses appear safe for both the mother and fetus.[18,40,68,80] Contraindications to prostaglandin E_2 cervical ripening include hypersensitivity to prostaglandins, cardiac disease, asthma, prior fundal uterine surgery, chorioamnionitis, and fetal compromise. Prostaglandin E_2 is advocated to prepare the unripe cervix for induction and thereby increase the likelihood that labor induction will be successful. Large-scale clinical trials of prostaglandin E_2, however, have not been done, and some openly question the efficacy of prostaglandin E_2 to shorten the duration of labor.[57]

The powerful contractions produced by prostaglandin F_2 alpha are useful to control postpartum hemorrhage due to myometrial atony and reduce postpartum blood loss. The intramyometrial injection of as little as 0.25 mg prostaglandin F_2 alpha (although 1.0 mg is generally recommended) either transcervically or transabdominally produces a sustained uterine contraction in approximately 4 minutes with few maternal side effects and is more effective than methylergonovine (Methergine) to control postpartum hemorrhage.[107] The prostaglandin analog, 15-methyl-prostaglandin F_2 alpha, can be safely administered systemically and is effective where prostaglandin F_2 alpha is ineffective.[24] The average onset time is 45 minutes.[49] Although oxytocin and ergonovine or methylergonovine remain the first agents used in the treatment of postpartum hemorrhage, the recommended treatment for control of postpartum hemorrhage in the presence of shock and continuing rapid blood loss is intramyometrial injection of 1.0 mg prostaglandin F_2 alpha or 0.25 mg 15-methyl-prostaglandin F_2 alpha. Less severe postpartum bleeding can be treated with 15-methyl-prostaglandin F_2 alpha, 0.25 mg, administered intramuscularly.

Tocolytics relax the myometrium. Although ritodrine is still the standard drug for treatment of premature labor, the beta-sympatomimetic agents have serious maternal side effects, including pulmonary edema,[4,12] myocardial ischemia,[113] cardiac arrhythmias,[36,109] cerebral vasospasm,[92] hypotension, and maternal metabolic changes.[24] This led obstetricians to reexamine the original work of Steer and Petrie on the efficacy of magnesium sulfate as a tocolytic agent.[105] Compared with the beta-sympathomimetics, ritodrine and terbutaline, magnesium sulfate was equivalent in efficacy with fewer maternal side effects.[11] Therefore, some advocate magnesium sulfate as the primary tocolytic agent.

Clinical trials of ritodrine and magnesium sulfate[115] in preterm labor patients sought a regimen that would lessen the cardiovascular side effects of the beta-mimetics and offer alternatives when beta-mimetics failed to inhibit labor. Pharmacologically, the two agents cause uterine smooth muscle relaxation by different mechanisms of action and may act complementary or synergistically. Routine adjunctive use of magnesium sulfate with ritodrine actually increased cardiovascular side effects,[35] but the addition of magnesium sulfate to ritodrine in those patients who failed ritodrine therapy alone, produced uterine tocolysis and prolonged the pregnancy.[48]

Indomethacin recently gained more acceptance as a tocolytic agent. Adverse effects on the fetus and neonate, reported in isolated cases, previously limited its use.[41,94] Two recent reports altered this limitation. The first was a small, carefully controlled clinical trial that reported that indomethacin was more effective than placebo in producing uterine tocolysis, with no adverse effects in the fetus or neonate.[79] The second was a retrospective, uncontrolled report of clinical experience using indomethacin in preterm labor patients with no adverse fetal or neonatal effects in 167 patients.[29] Use of indomethacin is increasingly advocated in carefully selected patients of less than 28 weeks gestation, who fail standard tocolysis and where fetal survival is questionable.[63]

There are conflicting reports on the use of calcium channel blockers as tocolytic agents. Verapamil, examined as a tocolytic agent, impaired A-V conduction before effecting uterine tocolysis.[78] Nefedipine, however, was effective as a tocolytic agent without adverse maternal or neonatal effects.[114] Recent reports of unexplained in utero fetal deaths in ewes who received calcium channel blockers caused those conducting clinical trials to be wary of similar problems in humans.

SUMMARY

This article reviewed newer drugs and techniques to control pain during labor, provide anesthesia for cesarean section, and control postpartum pain. PCA and epidural narcotics are now commonly used for pain after cesarean section. Ancillary drugs, used by both obstetricians and anesthesiologists, were discussed. The obstetric anesthesiologist can use this information to understand current trends in this area of anesthetic practice.

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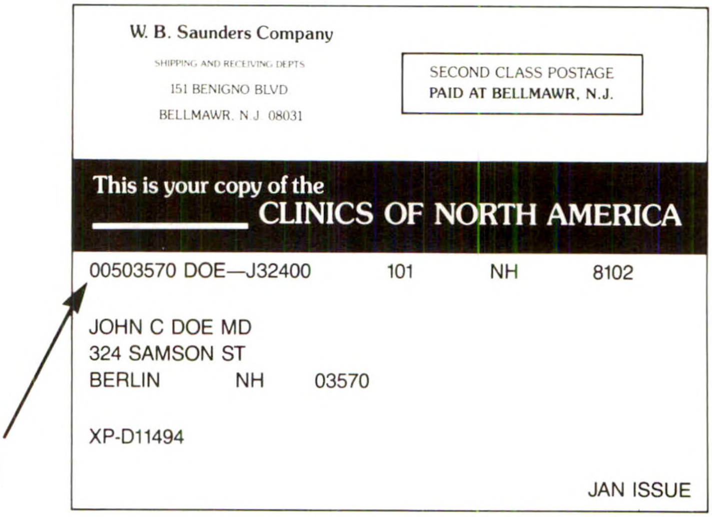

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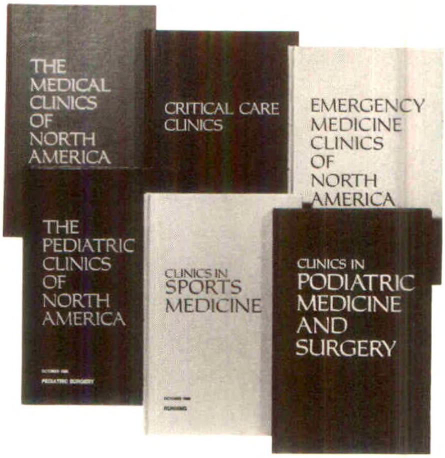
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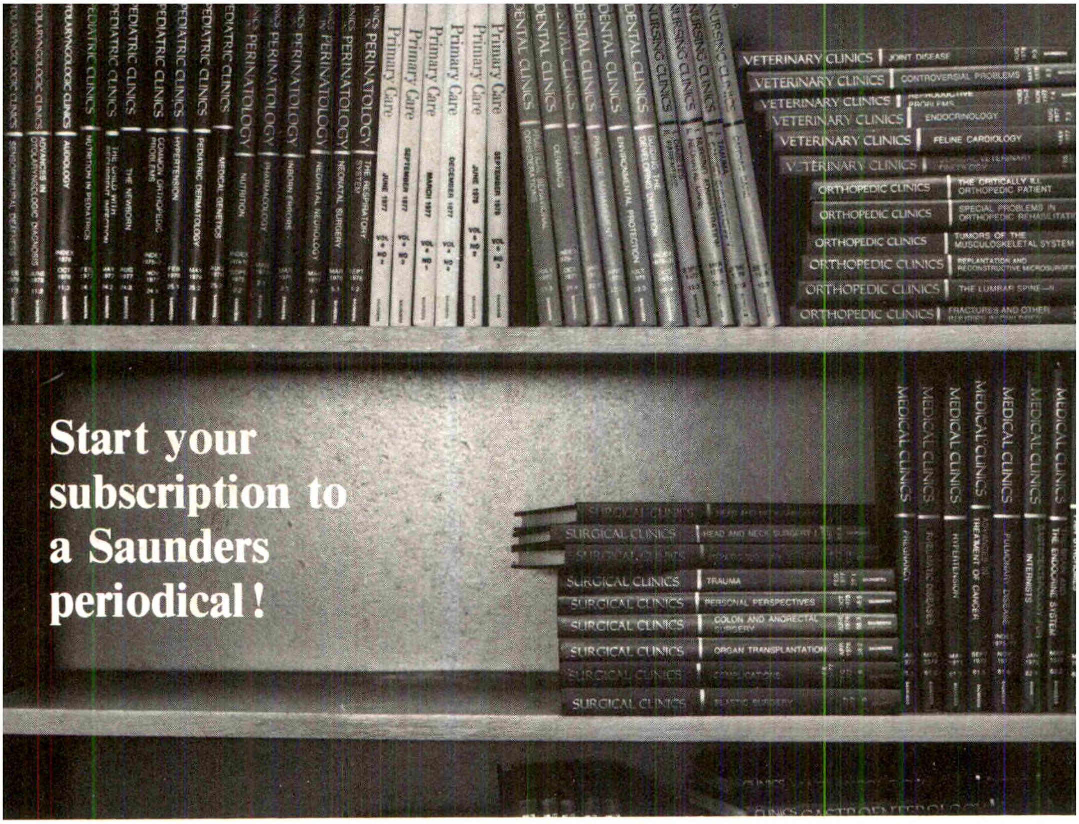

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